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Optimal Use Report

CADTH

Optimizing Health System Use of Medical Isotopes and Other Imaging Modalities

Supporting Informed Decisions

Optimizing Health System Use of Medical Isotopes and Other Imaging Modalities

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Authorship

Michelle Mujoomdar, Erin Russell, François Dionne, and Kimberlee Lambe were responsible for planning, authoring, and reviewing the report. Michelle Mujoomdar led the project team and was the liaison between MIIMAC and CADTH. Erin Russell, Kristen Moulton, and Christine Murray were responsible for authoring and revising select research reports. Erin Russell was responsible for reviewing cost estimates for all reports. Sarah McGill performed literature searches and verified bibliographic references.

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Conflicts of Interest

None declared.

INTRODUCTION

Medical isotopes, specifically technetium-99m (^{99m}Tc), are used in a variety of diagnostic imaging procedures involving approximately 24,000 Canadians every week.[1] Molybdenum-99, the precursor to ^{99m}Tc, is produced primarily at five large commercial reactors located in Belgium, Canada, France, the Netherlands, and South Africa.[2] The five reactors, commissioned between 45 and 55 years ago,[3] collectively supply 90% to 95% of the world's molybdenum-99.[2] Due to their advancing age, the reactors are experiencing an increasing number of scheduled (for maintenance) and unscheduled shutdowns, thereby making the production of molybdenum-99 unreliable.

According to a report to the Minister of Health from the Ad Hoc Health Experts Working Group on Medical Isotopes — formed in the midst of the nearly month-long unexpected shutdown of the National Research Universal (NRU) reactor in Chalk River, Ontario, in November 2007 — there were "enormous variations in how well or poorly Canada's nuclear medicine facilities fared during the 2007 shutdown of the NRU reactor."[4] The majority of Canada's supply of ^{99m}Tc is sourced from the NRU reactor — between 80% and 85% when the NRU is operational.[1]

In December 2008, the NRU reactor was again shut down unexpectedly, three days before planned scheduled maintenance, returning to service one week later.[5] Most recently, and of most significance, was the May 2009 to August 2010 outage, when the NRU reactor was unexpectedly off-line due to a leak in the reactor vessel.[2] Throughout the May 2009 to August 2010 outage, the supply of ^{99m}Tc was greatly reduced — with weekly supplies fluctuating significantly, depending on the province, region, or supplier.

It was as a result of the extended 2009-2010 shutdown of the NRU reactor that medical isotope production made headlines as a high-profile issue affecting patient access and requiring national action. In response, the Canadian government established an Expert Review Panel on Medical Isotope Production to assess the most viable options for securing supplies of ^{99m}Tc for the Canadian health care system over the medium- and long-term, and to identify any actions that might be required by governments and others to facilitate the realization of these options.[6]

In November of 2009, the panel submitted to the Minister of Natural Resources a report that contained a series of recommendations including "achieve better use of ^{99m}Tc supply through advanced alternative medical imaging technologies."[3] Following that, the Government of Canada developed an action plan to increase the security of the medical isotope supply for Canadians.[6,7]

The Government of Canada announced in January 2011 that it was investing in four projects to develop new ways of producing ^{99m}Tc.[8] The Non-reactor-based Isotope Supply Contribution Program was designed to advance cyclotron and linear accelerator technologies to achieve a more diverse and secure supply of ^{99m}Tc, with less reliance on nuclear reactor–based production.

In addition to the four non–reactor-based isotope projects, it was also announced that Health Canada was providing funding to the Canadian Agency for Drugs and Technologies in Health (CADTH) to "investigate the optimal use of medical isotopes and alternatives" and develop national guidance on how to optimize the management and use of ^{99m}Tc, and consider appropriate alternative medical isotopes and medical imaging equipment.[8] In 2009, Health Canada released a document titled *Guidance for Maximizing Supply of Technetium-99m (Tc-99m) During a Shortage*.[9] The guidance document was based largely on a disruption plan developed by the Government of Ontario. The goal of the CADTH project was to build on this existing guidance.

Most medical isotopes, unlike some other medical supplies, cannot be stockpiled because of their relatively short half-lives (half-life refers to the time it takes for the product to lose half its radioactivity). The half-life of molybdenum-99 is 66 hours and the half-life of its decay product, ^{99m}Tc, is six hours. Because it cannot be stockpiled, when there is a disruption in the supply of ^{99m}Tc, health care providers are faced with rationing a reduced supply. A 2010 paper by Rosenthal[10] discussed allocation of ^{99m}Tc when its supply is reduced and concluded that allocation decisions should be made by multi-disciplinary committees, using an ethical and transparent approach.

Throughout the life of the project, CADTH was advised by the specially created Medical Isotopes and Imaging Modalities Advisory Committee (MIIMAC).[11] MIIMAC was a 23-member pan-Canadian, multi-disciplinary committee consisting of institutional and regional representatives from health professions (nuclear medicine physicians, diagnostic radiologists, medical radiation technologists, cardiologists with expertise in cardiac imaging, a medical oncologist, a radiopharmacist, and a medical ethicist), administrators from ministries of health, and members of the public, as well as experts in scientific research and methodology. The composition of MIIMAC was chosen carefully and deliberately to allow for multiple perspectives, inclusive discussion and debate, and transparency in process.

ISSUE

Technetium-99m is the most widely used medical isotope in nuclear medicine and its supply is susceptible to shortages. Following the most recent supply disruption, which occurred from May 2009 to August 2010, CADTH was asked to develop national guidance on the optimal use of ^{99m}Tc in times of supply disruption.

OBJECTIVES

The purpose of this project was to provide national guidance on the optimal use of ^{99m}Tc during a situation of reduced supply. To accomplish this, our objective at CADTH was:

- to develop, taking a national perspective, a priority ranking of the most common clinical uses of ^{99m}Tc for use by decision-makers at various levels of the health system (i.e., institution, health authority, or jurisdiction) during a period of reduced supply of the isotope.

Early in the project, CADTH and MIIMAC acknowledged that a priority ranking constructed taking a national perspective will not accurately reflect the local contexts of all jurisdictions in which it is meant to be used. Given this, our second objective was:

- to design a customizable, web-based prioritization tool that allows decision-makers the opportunity to create personalized priority lists specific to their institution, health authority, or jurisdiction for use during a period of reduced supply of the isotope.

METHODOLOGY

Medical Isotopes and Imaging Modalities Advisory Committee

At the outset of this project, CADTH recognized the need to seek input from, and engage, experts in both medical imaging and the methodologies being used for the project. We also wanted additional perspectives, such as those of the public, to be represented.

MIIMAC was a purpose-built, project-specific committee with a term of less than two years. We actively recruited members who had experience on previous initiatives related to the shortages of ^{99m}Tc (e.g., Health Canada's Ad Hoc Health Experts Working Group, Natural Resources Canada's Expert Review Panel, and the Federal/Provincial/Territorial Working Group on Medical Isotopes). We did this specifically to leverage the experience of these individuals and also to ensure that we were avoiding duplication of effort. The 23-member committee was co-chaired by a nuclear medicine physician and a pediatric diagnostic radiologist. A list of MIIMAC members is available in Appendix 1.

In recruiting MIIMAC members, we worked to ensure that the committee had the appropriate expertise while also having national, geographic representation. Eight of the 10 provinces that conduct nuclear medicine imaging were represented on MIIMAC; nuclear medicine is not practised in any of the three territories.[12]

A professional facilitator was used for all committee meetings, which allowed the co-chairs to be full participants. Including the orientation meeting (held in October 2010), MIIMAC met four times (January 2011, April 2011, and January 2012). In addition, CADTH convened Working Groups (WG) — sub-groups comprising different MIIMAC

members who worked with the project team between meetings of the full MIIMAC. Three WG meetings took place (December 2010, March 2011, and November 2011). During the project period, the co-chairs and the project lead met 12 times via teleconference or web conference. One original MIIMAC member did not finish his term, leaving a 23-member committee for most of the term of the project. MIIMAC members were asked to declare any conflicts of interest before each full committee meeting. Any changes to declarations were reviewed by CADTH and by the co-chairs.

In lieu of voting, MIIMAC relied on debate and dialogue to ensure that all members had a level of comfort with each step before checking for consensus and proceeding to the next step. For our purposes, consensus was defined not as "Do you agree with it?", but rather, "Can you live with it?". No decision was final until the project lead, or a designate, followed up with any members who were absent from meetings. MIIMAC members were asked to complete a survey following each full committee meeting. The results of the surveys indicated that the vast majority of MIIMAC members were "extremely satisfied" with how meeting objectives were met, as well as with pre- and post-meeting communication.

Following each MIIMAC and WG meeting, the project team held debriefing sessions with the co-chairs and the facilitator, with a focus on implementing any suggestions for improvement.

Multi-Criteria Decision Analysis (MCDA)

We used a multi-criteria–based approach for the project. Multi-criteria decision analysis (MCDA) methodology was used to organize information and assist in the development of the priority list. MCDA was chosen based on the understanding that users of ^{99m}Tc and decision-makers considered multiple factors, or criteria, when allocating the isotope during the last supply disruption. These criteria included the severity of the condition being treated and the availability of potential alternative medical imaging modalities for tests that use ^{99m}Tc.

In general, MCDA involves the assessment of all possible courses of action on the basis of a common set of criteria. Thus, the two key elements of the MCDA process are the possible courses of action and the criteria. The possible courses of action are the universe of possible (i.e., implementable) choices for the decision-maker. The criteria represent a measurement tool for all the relevant considerations in the decision-making process. Relevant criteria therefore depend on the decision-making context.[13] Once all possible choices have been evaluated on the basis of the selected criteria, they can be equitably compared and conclusions can be formulated.

MCDA is a transparent and explicit process that, for this project, involved four basic steps adapted from an established priority-setting process.[13]

The first step was to develop relevant evaluation criteria. Each criterion has four components: name, definition, weight, and a rating scale, with an explicit definition of each rating point on the scale. The objective, in the development of criteria, is to include all considerations relevant to the decision that has to be made and to provide sufficient clarity to ensure consistency in the translation of information into ratings.

The second step was to identify the clinical uses of ^{99m}Tc requiring prioritization. Information supporting each criterion was incorporated into a single research report for each clinical use.

The third step was to formally evaluate the clinical uses of ^{99m}Tc using the information presented in the research report. This was done by rating each clinical use on each criterion and, using the criteria weight, calculating a composite score (i.e., weighted score). Given that the same criteria were always used, the weighted scores were comparable across all of the clinical uses.

The fourth and final step had two parts: validation and ranking. First, the weighted score for each clinical use was validated by MIIMAC to ensure that no process errors took place. Once validation was complete, each clinical use was ranked in relation to all the others to generate the priority list.

Identifying the relevant criteria

Development and refinement

MIIMAC members began the process of identifying criteria at their first face-to-face meeting (October 4, 2010). CADTH presented 13 criteria, based on data collected at the orientation meeting and follow-up correspondence, to the committee in January 2011. After review and discussion by MIIMAC, 11 evaluation criteria were identified. The criteria fall into two domains: those related to the underlying condition (Table 1) and those comparing either health conditions or ^{99m}Tc-based imaging and alternative imaging modalities that could be used in place of a ^{99m}Tc-based test (Table 2).

The criteria were posted on the CADTH website from March 22 to April 6, 2011, for stakeholder feedback. The feedback was considered by the CADTH project team. Based on the feedback received, there were no changes to the list of criteria after this date; however, minor changes were made to some of the criteria definitions to add clarity.

Table 1: Criteria Related to the Underlying Health Condition

Criterion	Definition
Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.

Table 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.

Table 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Clinical Uses	
Criterion	**Definition**
Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socio-economic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test who are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, and other burdens. This criterion does not include risks of adverse events, but is about everything related to the experience of undergoing the test.
Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Identifying the clinical uses of ^{99m}Tc to be prioritized

Recognizing that ^{99m}Tc is involved in the imaging of a broad range of medical conditions, and acknowledging that we would not be able to evaluate all uses of ^{99m}Tc, our objective was to create a priority list for those uses that accounted for a large proportion of the work that is done at most Canadian institutions. We used filter criteria to select the clinical uses for evaluation and, ultimately, for prioritization.

For the purposes of facilitating refinement of the clinical uses, the comprehensive list of possible conditions requiring ^{99m}Tc-based imaging was divided into five groupings based on body systems: cardiovascular, renal, musculoskeletal, gastrointestinal, and other body systems. Working in small groups, MIIMAC members were asked to refine the list of uses and capture the filter criteria that were used in the process. The following filter criteria were used: the impact of a ^{99m}Tc-based test on the management of the patient, number of ^{99m}Tc-based tests performed (also expressed as number of patients undergoing the imaging test), quantity of ^{99m}Tc used for each test, and acceptability of alternative imaging modalities to patients.

Development and refinement

Using the filter criteria described, MIIMAC developed an initial list of 22 clinical uses of ^{99m}Tc and possible alternatives or comparators (i.e., other nuclear and non-nuclear imaging tests) for possible prioritization. Following refinement by the project team and feedback from MIIMAC, 21 clinical uses of ^{99m}Tc were selected for evaluation and prioritization. Several important assumptions were made at this time:

- X-ray would be used as a first-line investigational tool, if appropriate
- Uses of ^{99m}Tc for which there were no reliable alternatives would receive priority and would be excluded from the analysis
- Patients for whom alternatives to the ^{99m}Tc-based imaging test were contraindicated (e.g., computed tomography [CT] involving contrast for patients with an allergy to the contrast agent or magnetic resonance imaging [MRI] for patients with some types of implantable cardioverter-defibrillators [ICDs]) would be prioritized to receive ^{99m}Tc.

Originally, two uses (Table 3) were identified that would be excluded from the prioritization process because there was no reliable imaging alternative to ^{99m}Tc. Therefore, in the event of a shortage of ^{99m}Tc, these clinical uses should be prioritized. The list of 21 clinical uses selected for evaluation was posted on the CADTH website from March 22 to April 6, 2011, for stakeholder feedback. The feedback was considered by the CADTH project team and no changes to the clinical uses were made based on the feedback received. However, subsequent to posting, and based on feedback from MIIMAC, several of the original 21 clinical uses were excluded from the prioritization process. These uses, and the reasons for exclusion, are tabulated (Table 3).

Table 3: Clinical Uses of ^{99m}Tc Excluded from the MCDA

Clinical Use	Reason for Exclusion	MIIMAC Recommendation
Evaluation of reflex sympathetic dystrophy	No reliable imaging alternative	Should be prioritized
Diagnosis of Meckel's diverticulum in pediatric	No reliable imaging alternative	Should be prioritized

Table 3: Clinical Uses of ^{99m}Tc Excluded from the MCDA		
Clinical Use	**Reason for Exclusion**	**MIIMAC Recommendation**
patients		
Imaging suspected cases of brain death	No reliable imaging alternative	Should be prioritized
Diagnosis of acute pyelonephritis in pediatric patients	Limited impact on management of condition; nuclear medicine is primarily used to assess scarring, not to diagnose pyelonephritis	Should not be prioritized
Evaluation of the limping child (excluding suspected cases of abuse)	Refers to various conditions accounted for elsewhere (i.e., osteomyelitis and fracture)	Should be considered in related reports (i.e., osteomyelitis and fracture)

MCDA = multi-criteria decision analysis; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; ^{99m}Tc = technetium-99m.

Summary of clinical uses, interventions, and comparators included in the MCDA

The final clinical uses included in the MCDA are listed in Table 4. Two of the clinical uses, evaluation of obstructive uropathy and diagnosis of osteomyelitis, were separated into distinct adult and pediatric patient populations. Three other clinical uses — diagnosis of fractures, imaging for metastatic disease, and evaluation of painful prosthesis — were subdivided: diagnosis of fractures was rated separately for osteoporotic fractures and stress fractures; imaging for metastatic disease was rated separately for cancers of the breast, lung, and prostate; and evaluation of painful prosthesis was rated separately for infection and for loosening. The final priority list includes 24 ranked clinical uses. These represent the greater part of the volume of the work that is done at most Canadian institutions and includes those procedures that are time sensitive.

Table 4: Clinical Uses, Interventions, and Comparators Included in the MCDA			
Body System	**Clinical Use**	**Intervention**	**Comparator(s)**
Cardiovascular	Detection of ischemia	Stress SPECT MPI	CTCA Stress Echo Stress MRI Stress PET Stress ^{201}TI-SPECT
	Assessment of prognosis post-myocardial infarction	Stress SPECT MPI	CTCA Stress Echo Stress MRI Stress PET Stress ^{201}TI-SPECT
	Preoperative assessment prior to vascular, non-cardiac surgery	Stress SPECT MPI	CTCA Stress Echo Stress MRI Stress PET Stress ^{201}TI-SPECT
	ICD decision-making	RNA	Echo MRI
	Assessment of drug-induced cardiotoxicity	RNA	Echo MRI

Table 4: Clinical Uses, Interventions, and Comparators Included in the MCDA			
Body System	**Clinical Use**	**Intervention**	**Comparator(s)**
Renal	Evaluation of renal function — post-transplant	Renal scintigraphy	U/S
	Evaluation of renal function — suspected obstructive uropathy (in children and adults)	Renal scintigraphy	MRU U/S
	Evaluation of renal function — renovascular hypertension	Renal scintigraphy	Catheter angiography CTA MRA U/S
Musculoskeletal	Diagnosis of acute osteomyelitis (in children and adults)	Bone scanning	CT ^{111}In-WBC MRI PET U/S
	Evaluation of painful prosthesis	Bone scanning	Arthrography PET ^{111}In-WBC
	Imaging for metastatic disease	Bone scanning	MRI PET
	Diagnosis of avascular necrosis	Bone scanning	MRI
	Diagnosis of fracture (osteoporotic and stress)	Bone scanning	CT MRI PET
Gastrointestinal	Detection of lower gastrointestinal bleeding	GI scintigraphy	Abdominal angiography
	Diagnosis of acute cholecystitis	Hepatobiliary scintigraphy	CT MRCP U/S
	Assessment of bile leak	Hepatobiliary scintigraphy	CT ERCP MRCP U/S
Other	Detection of pulmonary embolism	V/Q scan	CTPA
	Identification of the sentinel lymph node in patients with breast cancer	Radiopharmaceutical + blue dye	Blue dye alone ALND

ALND = axillary lymph node dissection; CT = computed tomography; CTA = computed tomography angiography; CTCA = computed tomography coronary angiography; CTPA = computed tomography pulmonary angiography; Echo = echocardiography; ERCP = endoscopic retrograde cholangiopancreatography; GI = gastrointestinal; ICD = implantable cardioverter-defibrillator; ^{111}In-WBC = indium-111–labelled white blood cells; MCDA = multi-criteria decision analysis; MPI = myocardial perfusion imaging; MRA = magnetic resonance angiography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; MRU = magnetic resonance urography; PET = positron emission tomography; RNA = radionuclide angiography; SPECT = single-photon emission computed tomography; ^{201}Tl = thallium-201; U/S = ultrasound; V/Q = ventilation/perfusion.

Generation of research reports to inform the MCDA process

A single research report was generated for each of the clinical uses. For the five clinical uses that were further refined (i.e., diagnosis of fracture, diagnosis of acute osteomyelitis, evaluation of painful prosthesis, imaging for metastatic disease, and suspected obstructive uropathy), the research reports were organized such that the information was presented separately for each population in a single report. Literature reviews were conducted for each of the clinical uses selected by MIIMAC. Each literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching MEDLINE with In-Process records via Ovid; The Cochrane Library; PubMed; and Canadian and major international health technology agencies, as well as focused Internet searches. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and diagnostic accuracy studies (primary studies of randomized and non-randomized design). Randomized controlled trials and non-randomized studies were also searched for all but two clinical uses (post-myocardial infarction and ischemia), due to the large volume of literature for these two clinical uses. The searches were limited to English-language documents. Regular alerts were established to update the search until October 2011. Search strategies are described in each research report (Appendix 2).

Targeted searches were done as required for the application of the criteria, using the databases listed above and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted. All fee codes used to inform the cost criterion were verified by experts.
The research reports contained a summary of the evidence and information relating to each of the criteria. All of the reports were reviewed by one to three MIIMAC members.

Producing a ranking

Assigning criteria weights

Once the list of clinical uses to be prioritized had been created and the evaluation criteria generated, MIIMAC assigned weights to the 11 criteria, to reflect their relative importance in the process of prioritization in a time of reduced supply of ^{99m}Tc. At the April 2011 meeting, MIIMAC began the weighting process first by clustering the criteria into high, medium, and low relative importance, with three to four criteria in the high and low clusters. This work was done in a small-group format to encourage and maximize dialogue.

MIIMAC used a simple approach that involved the allocation of 100 points to the 11 criteria. As a starting point, each cluster was given a total weight range — high relative importance (40 to 60 points), medium relative importance (20 to 40 points), and low relative importance (10 to 20 points). Once the criteria were mapped to the appropriate level of relative importance, MIIMAC members were asked to rank the criteria within each cluster (Figure 1). Using the rankings from each cluster, final weights were assigned (Table 5)

Figure 1: Weighting of the criteria

Cluster A — High relative importance (order of importance):
- Impact on mortality (1)
- Impact on morbidity (2)
- Timeliness and urgency (3)
- Diagnostic accuracy (4)

Cluster B — Medium relative importance (order of importance):
- Size of affected population (1)
- Accessibility (2)
- Health disparity (3)

Cluster C — Low relative importance (order of importance):
- Availability of expertise (1)
- Patient acceptability (2)
- Risk (2)
- Cost (3)

Table 5: Relative Importance of Criteria

Criterion	Weight
Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	16
Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	15
Timeliness and urgency of test results in planning patient management	14
Relative diagnostic accuracy of the test	12
Size of the affected population	9
Accessibility of alternatives (equipment)	8
Relative impact on health disparities	7
Relative availability of expertise and experience required for the test (personnel)	6
Relative acceptability of test to patients	5
Relative risks associated with the test	5
Relative cost of the test	3

Determining a rating for criteria

The tool used to rate each of the clinical uses of ^{99m}Tc against the 11 criteria is included in Appendix 3. Briefly, those criteria related to the underlying condition were permitted only positive values (range: 0 to +3), while criteria comparing ^{99m}Tc with an alternative imaging modality had negative or positive values (range: –3 to +3). Positive values were indicative of a situation in which the ^{99m}Tc-based imaging test outperformed the alternative, whereas a negative score indicated that the alternative test outperformed the ^{99m}Tc-based test. A rating of 0 was interpreted to mean that, for that particular criterion, there was no difference between the alternative test and the ^{99m}Tc-based imaging test.

Three iterations of ratings were done. First, the project team rated the reports (October 2011). Second, a two-day WG meeting was held in November 2011, at which the WG extensively reviewed the pre-ratings done by the project team. The WG, made up of six MIIMAC members, and the project team discussed each rating for all 24 clinical uses. There was an emphasis on ensuring consistency between like modalities across clinical

uses. For example, acceptability to patients of the ^{99m}Tc-based test versus MRI received the rating of –1 (i.e., the ^{99m}Tc-based test is minimally less acceptable than MRI); this rating was then repeated for other clinical uses that had similar patient populations. The project team made any necessary revisions to the reports based on feedback from the WG.

In addition to reviewing and revising the ratings and generating preliminary scores, the WG discussed the criterion of "relative impact on health disparities." For the purposes of this project, we considered the 24 underlying health conditions requiring ^{99m}Tc-based imaging and discussed possible health disparities for each condition.

Four factors that are associated with variations in health status include socio-economic status, Aboriginal identity, gender, and geographical location.[14] The WG discussed the criterion of relative health disparity extensively and concluded that this important criterion reflected extremely local issues. While it could be argued that this is also the case for other criteria, the WG suggested that to assess and rate health disparities at a national level would dilute any potential disparities at the local level. As such, the WG made the recommendation to the full MIIMAC that this criterion be rated only at the local level. We did, however, include any information identified in the literature review that addressed potential health disparities within each research report.

Finally, the full MIIMAC convened for two days in January 2012 in order to finalize the ratings and rankings of the clinical uses of ^{99m}Tc developed by the WG. MIIMAC members reviewed the reports prior to the meeting. The ratings proposed by the WG were mostly unchanged. Because each available alternative imaging modality had to be rated for each clinical use, a total of 482 ratings (i.e., a rating of 0 to 3 or –3 to +3 was selected for each criterion for each alternative modality to ^{99m}Tc-based imaging for all of the clinical uses) based on the evidence and information identified were finalized by MIIMAC. MIIMAC accepted the recommendation of the WG to score the health disparities criterion at the local level.

After the ratings for each criterion for all 24 clinical uses were finalized, those ratings were multiplied by the corresponding weight for the criterion to generate a weighted score. For each clinical use, the weighted scores (rating assigned to a diagnostic alternative modality for a particular criterion multiplied by the weight of the criterion decided by MIIMAC) for the 11 criteria were summed to calculate a composite weighted score for each alternative modality. A total of 63 composite weighted scores were calculated. The placement of the clinical use in the priority ranking was determined by selecting the alternative to the ^{99m}Tc-based test with the lowest weighted composite score for each use. The lowest score was selected because the closer a score is to 0, the more closely the alternative resembles the ^{99m}Tc-based imaging test on the basis of the 11 criteria used in the analysis and, therefore, the more appropriate it is to use the alternative if there is a shortage of ^{99m}Tc.

Achieving consensus

The final ranking, based on the ratings agreed to by MIIMAC, was shown to members. As part of the validation, the meeting facilitator asked each committee member, "Do you support the ranked list?" Permissible responses were: "I agree," "I am still undecided," or "I disagree."

RESULTS

A total of 18 clinical uses of ^{99m}Tc were selected to be prioritized. Five of the clinical uses were further refined (i.e., diagnosis of fracture, diagnosis of acute osteomyelitis, evaluation of painful prosthesis, imaging for metastatic disease, suspected obstructive uropathy), resulting in a priority ranking of 24 uses of the isotope. A final priority ranking was generated based on the best alternative test to the ^{99m}Tc-based test. The ranking reported in Table 6 represents a prioritization list developed using a national perspective, assuming the availability of the next best alternative. Should the next best alternative not be available, a complete list of alternatives (and their weighted scores) is presented in Appendix 4. It is important to note that many of the weighted composite scores between uses and, indeed, between alternatives for a single use were very close. A complete list of the ratings for all the alternatives is provided in Appendix 5. The cut-offs for distinct clusters were not obvious and a discussion between end-users of the priority ranking must take place to determine what constitutes a true difference in scores. This process is not intended to be used as a "calculator"; rather, the intent is to collect and organize information and summarize it in a consistent manner.

The results of the national analysis by MIIMAC indicate that, in the event of a disruption in the supply of ^{99m}Tc, clinical uses with high scores (e.g., detection of lower gastrointestinal bleeding) have relative high priority, while clinical uses with lower scores (e.g., detection of stress fracture) are of relative lower priority.

Table 6: Priority Ranking of Uses of ^{99m}Tc

Clinical Use	Score	Next Best Alternative (If Available)
Detection of lower GI bleeding	200	AA
Assessment of bile leak	139	U/S
Detection of pulmonary embolism	135	CTPA
Diagnosis of (osteoporotic) fracture	132	MRI
Diagnosis of acute osteomyelitis (children)	131	CT
Imaging for metastatic disease (breast)	125	^{18}F-PET
Imaging for metastatic disease (lung)	118	^{18}FDG-PET
Assessment of prognosis post-myocardial infarction	117	Echo
Detection of ischemia	117	Echo
Imaging for metastatic disease (prostate)	113	^{18}F-PET
Preoperative assessment prior to vascular, non-cardiac surgery	108	Echo
Evaluation of painful prosthesis (loosening)	101	Arthrography
ICD decision-making	99	Echo
Diagnosis of acute cholecystitis	96	U/S
Evaluation of renal function — post-transplant	90	U/S
Evaluation of painful prosthesis (infection)	85	^{111}In-WBC
Assessment of drug-induced cardiotoxicity	82	Echo
Diagnosis of acute osteomyelitis (adults)	72	MRI
Diagnosis of avascular necrosis	70	MRI
SLNB*	67	Blue dye
Suspected obstructive uropathy (adults and children)	64	U/S
Suspected obstructive uropathy (adults and children)	64	U/S
Evaluation of renal function — renovascular hypertension	62	U/S

Table 6: Priority Ranking of Uses of ^{99m}Tc		
Clinical Use	**Score**	**Next Best Alternative (If Available)**
Diagnosis of (stress) fracture	57	MRI

AA = abdominal angiography; CT = computed tomography; CTPA = computed tomography pulmonary angiography; Echo = echocardiography; ^{18}F = fluoride; ^{18}FDG = fluorodeoxyglucose; GI = gastrointestinal; ICD = implantable cardioverter-defibrillators; ^{111}In = indium-111; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRU = magnetic resonance urography; PET = positron emission tomography; SLNB = sentinel lymph node biopsy; ^{99m}Tc = technetium-99m; U/S = ultrasound; WBC = white blood cells.

* Assumes that using blue dye alone is a viable alternative.

DISCUSSION

Summary

The purpose of this project was to provide national guidance on the optimal use of ^{99m}Tc during a situation of reduced supply. While there are a number of ways that the supply of ^{99m}Tc could be optimized, the focus of this project was on prioritization. We developed a framework by which relevant factors to be considered when allocating ^{99m}Tc can be combined to create a priority ranking.

Technetium-99m is used in the diagnosis or management of a wide array of conditions — from cardiac imaging, to evaluation of renal function in patients who received kidney transplants, to detection of a fracture. We acknowledged that we would not be able to prioritize all uses of ^{99m}Tc; however, we wanted to select a group of uses that account for the majority of patients who would be seen at nuclear medicine departments within Canadian hospitals.

A total of 24 clinical uses were selected for the prioritization process. The 24 uses were evaluated against 11 criteria that were developed by CADTH and MIIMAC. The criteria represent factors that should be considered when allocating the isotope during a period of reduced supply and are reflective of the varied perspectives on MIIMAC. For each of the uses, a research report was generated. Each report provided a summary of evidence found relating to each of the 11 criteria. Overall, the amount and quality of the related evidence varied between criteria and between clinical uses. The use of MCDA allowed for the comparison of very different clinical uses using the same framework.

Importantly, MIIMAC discussed the implementation of a priority ranking in a real-world clinical setting. Practically, when the available supply of ^{99m}Tc is reduced, the isotope would be allocated according to the priority list — first to high-priority clinical uses. Any remaining isotope activity at day's end would be allocated in similar manner, recognizing that some uses may require more of the isotope than what is remaining. In this instance, that particular clinical use would be skipped and the residual isotope would be used for the next use in the priority ranking for which there is adequate activity.

The guidance[9] developed previously by Health Canada and based on a disruption plan produced by the Government of Canada provided a number of suggestions to maximize the use of the existing supply of ^{99m}Tc. These included using a lower dose of the isotope and scanning for a longer period of time, adjusting the scheduling of procedures to allow for more efficient use of the ^{99m}Tc generator, using alternative imaging procedures, and

prioritizing patients who will receive the isotope. An explanation of the methodology used to develop the existing guidance was not available.

With respect to prioritization, the Health Canada guidance focused largely on urgent medical need as a driver for priority. No rank-order was provided and the majority of the clinical uses listed as “Priority Needs for Tc-99m” are uses for which an alternative is either not available or is contraindicated. Clinical uses of ^{99m}Tc for which there was no alternative, or the alternative(s) were not appropriate for a particular patient population, were not included in our prioritization process. Indeed, our group concluded that such uses should receive priority allocation and our project addressed the use of ^{99m}Tc beyond these “must do” uses.

The one notable difference between our priority list and that distributed by Health Canada is the use of ^{99m}Tc-based imaging to identify the sentinel node, and thereby provide information related to stage, in patients newly diagnosed with breast cancer. It is important to note that our process identified two alternative approaches to identifying the sentinel node — the use of blue dye alone and removal of all axillary nodes (axillary lymph node dissection; ALND).

In our analysis, the blue dye alone was rated as a relatively strong alternative to the ^{99m}Tc-based test; however, we acknowledge that at some institutions, this may not be a viable alternative. In this circumstance, ALND would be the only alternative. Given that ALND was rated as a less favourable alternative to the ^{99m}Tc-based test, at these institutions, identification of the sentinel node would likely receive higher priority.

Web-based prioritization tool

While the primary objective of the project was to develop, using a national perspective, a priority ranking of the most common clinical uses of ^{99m}Tc for use during a period of reduced supply, we recognized that some criteria such as the availability of alternatives, and health disparities, as well as the relative importance of the criteria, will differ between jurisdictions in Canada.

To that end, we are creating a web-based prioritization tool. The web tool will enable decision-makers to identify, from the national ranked list, the clinical uses of ^{99m}Tc applicable at their institution, as well as the alternative imaging modalities available. The tool will also allow for the re-weighting of the criteria, making the evaluation reflective of their local environment.

The output of the tool will be a site-specific, ranked list of clinical uses requiring ^{99m}Tc that can be used to assist local prioritization during a supply disruption and that is consistent with the national ranked list. A ranked list of alternative medical imaging modalities for each clinical use that can be used in lieu of ^{99m}Tc-based imagining will also be generated. Once complete, organizations can review or revise their customized priority list at any time – most importantly when there are major changes (e.g., new equipment, new procedures, new information, etc.).

A key component of this project was the involvement of individuals who provided unique perspectives on not only the development of the criteria, but also regarding the relative importance of the criteria. While the process can be completed by one or more

individuals who share a similar perspective (e.g., physicians from one department or administrators within a health region), it is strongly encouraged that as many as possible of the perspectives from those either involved with or affected by the allocation of ^{99m}Tc be involved in the process. The intent is for users of the tool to work collaboratively with key decision-makers within hospitals, health authorities, and jurisdictions to create a customized priority ranking that is reflective of their local setting. The tool will be available on the CADTH website after the report is finalized.

Strengths and Weaknesses of this Assessment

To allow for optimal committee dynamics, we were cognisant of its size, ensuring the composition of MIIMAC was comprehensive, but not exhaustive. For example, non-academic hospitals were less represented, some groups of referring physicians were not represented, and expertise of an adult radiologist specializing in CT and MRI would have been beneficial.

MCDA provides a transparent and explicit basis for decision-making and a framework for combining decision-makers' values and preferences with researcher measurement of performance.[15] The use of MCDA methodology in this assessment represents an innovative approach to an allocation decision. To our knowledge, this is the first instance in which MCDA has been used to prioritize patient populations. This approach also promotes consistency — within hospitals and within health authorities or jurisdictions — in how patients are prioritized and ultimately, who receives a ^{99m}Tc-based test during shortage situations.

The criteria used to evaluate the selected clinical uses and their alternative imaging modalities were chosen after extensive dialogue between key members of the medical decision-making community — practitioners, patients, and hospital administrators. This should ensure that the report and its findings are relevant to the end-users of the final product. The criteria were weighted according to their importance in the decision-making process by MIIMAC members. Care was taken to ensure that all committee members had a high level of comfort with each step of the process before proceeding.

To ensure consistency in how the clinical uses and their alternatives were rated, the ratings were validated first by a WG and then by MIIMAC. The scarcity of data to inform some of the criteria is a limitation of the assessment. In addition, because of the timelines associated with the project, we limited inclusion of studies for those six criteria requiring comparison of the ^{99m}Tc-based test directly to an alternative imaging modality to studies making direct comparisons. This approach likely resulted in the exclusion of studies that may have further supported or contradicted our findings for a particular criterion. However, each report was reviewed by at least one clinical expert on MIIMAC.

Generalizability of Findings

The priority ranking presented in this report is from the national perspective, and thus should be considered somewhat generalizable across the country. MIIMAC consisted of representatives from eight different jurisdictions (British Columbia, Alberta, Saskatchewan, Manitoba, Ontario, Quebec, Nova Scotia, and Newfoundland). We strove for representation from both academic and non-academic hospitals; however, the composition of the committee does favour those who work at larger centres.

CADTH and MIIMAC recognize that there is significant variation in, among other things, the availability of alternatives, the availability of expertise, and the impact on health disparities from one jurisdiction to another, making it difficult to produce a national report that is truly generalizable. For this reason, an output of our work is the accompanying web-based prioritization tool that was developed to allow decision-makers to conduct customized analyses at the local level. The results of the customized analysis should be appropriate to the population of interest.

Knowledge Gaps

The lack of high-quality evidence regarding the diagnostic imaging procedures assessed in this project was a significant challenge to the production of the research reports used to inform the MCDA process. Where evidence from peer-reviewed published sources or the grey literature was not identified, we relied on expert opinion. Given more time, certain data could likely have been acquired through survey methods. Select knowledge gaps are highlighted in Table 7.

Table 7: Evidence Base

Criterion	Knowledge Gaps
Size of the affected population	Surveillance is common in the realm of infectious disease, but point prevalence estimates were not available for the clinical conditions included in this report.
Impact on health disparities	While health disparity reduction has been a health sector priority for decades,[14] we struggled to find data for any of the population groups identified as having a disproportionate burden. In the absence of these data, no informed comment could be made as to whether a supply disruption would reduce or increase health disparities.
Relative acceptability of the test to patients	Few studies[16,17] have investigated the acceptability of ^{99m}Tc-based tests, compared with the alternatives, from the patient's perspective. The two referenced in the evidence reports prepared by CADTH included 41 patients and 63 patients, respectively.
Relative diagnostic accuracy of the test	The bulk of the evidence presented to MIIMAC was about the diagnostic accuracy of the various tests. However, the evidence base is not as robust as it is for other health technologies, such as pharmaceuticals.
Relative risks associated with the test	There were discrepancies in the reported radiation dose associated with the nuclear and non-nuclear diagnostic imaging procedures being evaluated.
Relative availability of expertise and experience required for the test	This criterion was informed primarily by expert opinion. While the NPS captures the number of physicians and specialists in Canada, expert judgment was required to estimate how many of a given specialty might have the expertise required to perform a given procedure. For select non-imaging alternatives, some published information was available regarding competency to perform the procedure.
Accessibility of alternatives	This criterion was informed primarily by expert opinion. While the number of devices across the country, province, and territory is made available by CIHI, expert judgment was required to estimate the capacity of the system to accommodate increased demand for the alternatives.

CADTH = Canadian Agency for Drugs and Technologies in Health; CIHI = Canadian Institute of Health Information; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; NPS = National Physician Survey; ^{99m}Tc = technetium-99m.

CONCLUSIONS AND IMPLICATIONS FOR DECISION-MAKING

Recent global shortages in the supply of the medical isotope prompted Health Canada to request that CADTH produce national guidance on the optimal use of ^{99m}Tc. While there are a number of strategies that can be taken to optimize the use of the isotope — many of which were employed during the last supply disruption — the focus of our work is optimal allocation through prioritization in the event that the supply of ^{99m}Tc is scarce.

Working with a multi-disciplinary committee comprising experts in research methodology, health economics, institutional and regional representatives from health professions (nuclear medicine physicians, radiologists, technologists, cardiologists, a medical oncologist, a radiopharmacist, a medical ethicist), administrators from ministries of health, and members of the public, we developed a framework using a multi-criteria–based approach by which relevant factors to be considered when allocating ^{99m}Tc can be combined to create a priority ranking of clinical uses of the isotope.

The ultimate result of the process is a prioritized list of clinical uses of ^{99m}Tc that is backed by an explicit methodology that organizes all relevant information. Since the process is explicit, results can be explained, or adjusted to allow for changes in the relevant information (e.g., acquisition of new equipment or changes to wait times for imaging procedures). When the available supply of ^{99m}Tc is reduced, the isotope would be allocated first to high-priority clinical uses.

The list of clinical uses that require ^{99m}Tc-based imaging is not exhaustive. Its intent is to assist health care practitioners and decision-makers in managing a large proportion of the work they would see within their institution(s) during a time of reduced supply. Importantly, uses of ^{99m}Tc for which no reliable alternative exists were not formally included in the prioritization process because they should be allocated ^{99m}Tc, if available.

We strove to include the most relevant alternatives to ^{99m}Tc-based imaging, which typically included other radioisotopes, CT, MRI, PET, and U/S. We did not include modalities or approaches that were under investigation. In some jurisdictions, select alternative imaging modalities may be unavailable. In addition, wait times for imaging modalities in some jurisdictions may already be long, or there may be restrictions on the ordering of some of these modalities by family physicians. Institutions, health authorities, and jurisdictions may wish to consider measures to increase access to these imaging modalities, such as an extension to the hours the scanners are in operation or changes to ordering privileges.

The output of this project, the national guidance, has become the foundation for a flexible web-based tool that can be customized for local use. Ideally, users of the web-based tool will work collaboratively with key decision-makers at their level to create a customized priority ranking that is reflective of their local setting – be it a hospital, a health authority, or a jurisdiction, and consistent across the country.

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APPENDICES

Appendix 1: Members of the Medical Isotopes and Imaging Modalities Advisory Committee (MIIMAC) as of March 2012

Patrick Au
Dr. Robert Beanlands
Dr. Charles Butts
Gazira Chan
Susan Delaney
Dr. Sandor Demeter
Dr. Terry Ell
Dr. Dean Fergusson
Heather Gibson
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Dr. Norman Laurin
Dr. Ted Lyons
Dr. Gilbert Matte
Dr. Sandy McEwan*
Dr. Craig Mitton
Christine Preece
Jean Pruneau
Dr. Martin Reed*
Dr. Terrence Ruddy
Rick Scanlan
Dr. Lisa Schwartz
Dr. Eric Turcotte
Dr. George Wells

*Indicates a position of co-chair.

Appendix 2: Research reports

APPENDIX 2.1

INDICATION OVERVIEW

A lower gastrointestinal (GI) bleed (LGIB) is defined as acute or chronic bleeding from the colon or anorectum (distal portion of digestive tract including the anal canal and distal few centimetres of the rectum.[1] LGIB accounts for 20% to 25% of all cases of GI bleeding.[1,2] Causes for LGIB are numerous and can be anatomic (e.g., diverticular disease, Meckel's diverticulum), vascular (e.g., ischemia), traumatic, inflammatory (e.g., colitis, Crohn's disease), or neoplastic (e.g., small-bowel tumours).[1] Factors contributing to development of LGIB include advanced age and use of non-steroidal anti-inflammatory agents.[3] Acute bleeding stops spontaneously in 85% of patients with LGIB.[1,3]

Colonoscopy is the diagnostic procedure of choice for acute and chronic bleeding; angiography is used if colonoscopy fails or cannot be performed.[1,4] Nuclear imaging is used for cases of unexplained intermittent (i.e., slow) bleeding, when colonoscopy or angiography fail to detect the source of bleeding.[1] Technetium-99m(^{99m}Tc)–labelled erythrocytes can detect bleeding at a rate of 0.1 to 5 mL/minute, thus showing blood flow and localizing the area of the bleeding.[4] The detection of bleeding sites might be difficult due to the intermittent nature of bleeding.[5,6] This may lead to a delay in treatment and result in morbidity and mortality.[2]

Population: Patients with suspected lower gastrointestinal bleeding.

Intervention: ^{99m}Tc active bleeding scintigraphy (scan).

Radionuclide scans have been used for localization of LGIB since the 1970s.[7] This test uses serial images following an intravenous bolus injection of radiopharmaceuticals.[8] Two radiopharmaceuticals are used for this purpose: ^{99m}Tc-sulfur colloid (SC) and ^{99m}Tc-labelled red blood cells (RBCs).[7,9-11]

In ^{99m}Tc-SC technique, the radiotracer is used in early phase vascular imaging. The theoretical consideration behind this technique is that ^{99m}Tc-SC is rapidly cleared from the circulation by the liver, spleen, and bone marrow (half-life 2.5 minutes to 3.5 minutes), whereas extravasated radio-labelled blood in the GI tract will not be cleared as rapidly and will stay in the GI tract. Therefore, a higher contrast can be seen between the location of extravasated blood and the diminishing background activity.[9,10] The main limitation of this technique is that the radiopharmaceutical remains in circulation for 10 to 15 minutes only, so that detection of the bleeding site is not possible after this time period.[9]

^{99m}Tc-labelled RBCs remain in circulation for a longer period of time and are the most commonly used radiopharmaceutical for detection of GI bleeding.[9-11] This technique allows for the detection and localization of intermittent bleeding.[9] In addition, small amounts of bleeding can be detected by ^{99m}Tc-labelled RBCs, because this method is sensitive to low rates of bleeding (0.1 mL/minute to 0.5 mL/minute).[12] Acquisition of single-photon emission computed tomography (SPECT) or hybrid SPECT/ computed tomography (CT) images with ^{99m}Tc-labelled RBC scan is shown to be helpful in the detection of bleeding sites.[8,13]

Other ^{99m}Tc-based radiopharmaceuticals such as ^{99m}Tc-labelled albumin and ^{99m}Tc–heat-damaged RBCs have also been studied for scintigraphic diagnosis of LGIB.[14]

Comparators: For this report, abdominal angiography is considered an alternative to ^{99m}Tc scintigraphy (scan).

- *Abdominal angiography:* This is an invasive diagnostic test for detection of LGIB. Angiography has traditionally been used to guide surgical resection, but it also can be used for therapeutic purposes through pharmacologic vasoconstriction or micro-embolization.[7,15] This test uses a contrast agent to study mesenteric and celiac arteries (branches of abdominal aorta) through X-ray exploration. A positive angiogram is defined as the extravasation of contrast agent to the lumen of the intestine.[16] For an angiogram to be positive, bleeding needs to be active and greater than 0.5 mL/minute at the time of the study.[7,12]

Other new techniques, such as CT-angiography (helical CT after injection of a contrast agent) or magnetic resonance (MR) angiography (magnetic resonance imaging [MRI] with an intravascular contrast agent) have also been used for detecting LGIB.[5,17]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and gastrointestinal hemorrhage.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. No date or human limits were applied to the HTA/SR/MA search. For primary studies, the retrieval was limited to documents published between January 1, 1996 and March 1, 2011, and the human population. Both searches were also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

There were eight potential clinical articles identified through the MA/SR/HTA filtered search and two were subjected to full-text review. Two hundred and thirty one potential primary studies were identified with the primary studies search. Additional studies were identified in searches for grey literature, targeted searches, and alerts.

No relevant systematic reviews and meta-analyses were included through this search. One systematic review, identified through the grey literature search, was included and used to abstract data on the diagnostic accuracy of ^{99m}Tc scintigraphy.[18]

No randomized controlled trials reporting on the accuracy of diagnostic tests of interest, patient outcomes, or quality of life were found. Nine observational studies reported on the diagnostic accuracy of the alternative tests of interest.[15,19-26] Of these, two studies were excluded due to lack of comparison to a confirmatory or gold standard test,[15,26] and the remaining seven studies were retained. Two of the included primary studies,[24,25] along with two additional qualitative review articles found by the search,[27,28] summarized the results of older observational studies on diagnostic accuracy of either ^{99m}Tc scintigraphy or abdominal angiography (Appendix 4).

The remaining articles from the database searches, along with other articles found through searching the grey literature, articles from the targeted searches, or articles from the reference lists of the identified potential articles, were used to abstract information regarding the rest of the criteria. When no literature was identified addressing specific criteria, experts were consulted.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	The annual incidence of hospitalization (considered an estimation of incidence) for LGIB has been estimated to be 20 to 30 per 100,000 persons in the US.[1,7,8,12,13,29] Assuming the incidence rate in Canada is similar to that of the US, this corresponds to more than 1 in 10,000 (0.01%) and less than or equal to 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	The timely detection and accurate localization of bleeding sites are essential for the guidance of treatment in high-risk patients.[2,9,11,19] According to the Saskatchewan hospital guidelines, radionuclide scans for detection of acute GI bleeding should be performed within 24 hours of the request (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). Test results have a significant impact on the management of the condition or the effective use of heath care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	Mortality is reported in 2% to 4% of patients with LGIB.[1,3,13] Early diagnosis of patients with severe bleeding, and early therapeutic interventions, lead to lower mortality rates.[13] Diagnostic imaging results can have minimal impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	No studies investigating the impact of scintigraphy or angiography on health outcomes or quality of life in patients with LGIB were identified, although between 5% and 50% of patients with persistent LGIB require surgical interventions.[7] Failure to diagnose and treat chronic LGIB results in chronic anemia, which does affect quality of life and also can cause anxiety (MIIMAC expert opinion). Diagnostic imaging results can have moderate impact on morbidity or quality of life.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>5</td><td>Relative impact on health disparities</td><td>To be scored locally.</td></tr>
<tr><td>6</td><td>Relative acceptability of the test to patients</td><td>GI Scintigraphy: Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

Abdominal angiography: Patients undergoing X-ray angiography may have concerns over radiation exposure and injection of contrast material.

^{99m}Tc-GI scintigraphy is significantly more acceptable to patients than abdominal angiography.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>No studies comparing the diagnostic accuracy of scintigraphy to CT-angiography or MR-angiography were identified. The included systematic review reported a pooled sensitivity rate of 62% for scintigraphy.[18]

There was a noticeable heterogeneity between the seven included primary studies,[19-25] regarding patient population, scintigraphy techniques, and reference standard. No studies comparing the diagnostic accuracy of scintigraphy to CT-angiography or MR-angiography were identified.

<table>
<tr><th colspan="5">Diagnostic Accuracy</th></tr>
<tr><th>Test</th><th>Reference</th><th>Type of Evidence</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>^{99m}Tc-scan</td><td>Abdominal angiography</td><td>SR and Obs</td><td>50.0 to 79.0</td><td>30.0 to 66.7</td></tr>
<tr><td>Abdominal angiography</td><td>Surgery/clinical follow-up</td><td>Non-SR review</td><td>40.0 to 86.0</td><td>NA</td></tr>
</table>
NA = not available; Obs = observational studies; SR = systematic review; ^{99m}Tc = technetium-99m.

Nuclear medicine tests can be performed over a longer observation period, thus increasing the likelihood that bleeding will be present at the time of testing (MIIMAC expert opinion).

Overall, the diagnostic accuracy of ^{99m}Tc-based scintigraphy is significantly better than abdominal angiography.</td></tr>
</table>

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>
Non–radiation-related Risks

^{99m}Tc-scintigraphy for GI bleeding: ^{99m}Tc-scintigraphy is non-invasive and associated with no morbidities or mortalities.[2,22] On rare occasions, allergic reactions to radiopharmaceuticals used for scintigraphy may occur.[12,32]

Abdominal Angiography: This is an invasive procedure, with a potential for major complications, particularly in the elderly and in patients with comorbid illness.[12,28] AEs are reported in 0% to 26% of patients undergoing angiography.[2,7,28] The most common complication is hematoma or bleeding at the catheter site.[7] Other potential AEs include arterial dissection, catheter site infection, loss of pulses in the lower extremity, and allergic reactions to the contrast agent.[2,7,12,28] More contrast is needed for the imaging of LGIB than for many other tests (MIIMAC expert opinion).

Radiation-related Risks

Both abdominal scintigraphy and angiography expose the patient to ionizing radiation. The average radiation exposure is higher for angiography than for GI bleeding scintigraphy.[33]

<table>
<tr><th colspan="2">Average Effective Doses of Radiation</th></tr>
<tr><th>Procedure</th><th>Average Effective Dose (mSv)</th></tr>
<tr><td>GI scintigraphy</td><td>7.8[33]</td></tr>
<tr><td>Abdominal angiography</td><td>12[33]</td></tr>
<tr><td>Average background dose of radiation per year</td><td>1 to 3.0[34-36]</td></tr>
</table>
GI = gastrointestinal; mSv = millisievert.

^{99m}Tc-based GI scintigraphy is significantly safer than abdominal angiography.
</td></tr>
<tr><td>9</td><td>Relative availability of personnel with expertise and experience required for the test</td><td>
As of 2006 in Canada, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, and 1,781 nuclear medicine technologists. Yukon, Northwest Territories, and Nunavut did not have the available personnel to perform and interpret tests to image lower GI bleeding. Other jurisdictions (e.g., Prince Edward Island) may offer limited nuclear medicine services.

Overall, the availability of health professionals to evaluate LGIB is good; however, a specialized centre to perform abdominal angiography may be required.
</td></tr>
</table>

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>Assuming the equipment is available, if GI scintigraphy using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that 25% to 74% of the procedures can be performed in a timely manner using abdominal angiography.</td></tr>
<tr><td>10</td><td>Accessibility of alternative tests (equipment and wait times)</td><td>Equipment: As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[32] There were 179 angiography suites for an average of 5.5 suites per million people.[37]

Wait times: In 2007, the latest year for which data are available, the average time for nuclear medicine examinations at MUHC hospitals was five days. However, the wait times were reported to be less than one day for emergency cases.[38] In the same year, wait times of angiography procedures at MUHC hospitals were 21 days in general, and less than 12 hours for emergency and urgent cases.[38]

A specialized centre may be required to perform abdominal angiography.

Assuming the necessary expertise is available, it is estimated that between 25% to 74% of procedures can be performed in a timely manner using abdominal angiography.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of ^{99m}Tc-labelled RBC scintigraphy is $239.80. Abdominal angiography is a significantly more costly alternative.

Relative Costs
Test | <b>Total Costs ($) | Cost of Test Relative to ^{99m}Tc-based Test ($)
RBC scintigraphy | 239.80 | Reference
Abdominal angiography | 898.86 | 659.06</td></tr>
</table>

AE = adverse event; CT = computed tomography; GI = gastrointestinal; LGIB = lower gastrointestinal bleed; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; MR = magnetic resonance; MUHC = McGill University Health Centre; RBC = red blood cells; ^{99m}Tc = technetium-99m; US = United States.

CRITERION 1: Size of affected population (link to definition)

The reviewed literature consistently considered acute bleeding requiring hospitalization in the estimation of LGIB incidence.

The annual incidence of hospitalization for LGIB has been estimated to be 20 to 30 per 100,000 persons in the United States.[1,7,8,12,13,29] The corresponding rate was not available for Canada.

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Although approximately 85% of LGIB cases are self-limited, improving without treatment, timely detection and accurate localization of bleeding sites to prevent the development of serious complications is essential for the treatment of the remaining 15% of patients.[2,9] Additionally, localization of LGIB site can be helpful in the selection of the initial catheter placement at angiography and guidance of a surgical resection, if necessary.[11,19] The time of diagnosis has been reported to be an important determinant of outcome in acute LGIB.[2]

Compared with angiography or colonoscopy, ^{99m}Tc-labelled RBC scans are easier to perform and need no patient preparation.[5] The use of scintigraphy can minimize the potential delays in the diagnosis of LGIB.[2] However, patients with massive LGIB usually undergo emergency angiography to localize and control the bleeding through appropriate therapeutic interventions during angiography.[5]

According to the Saskatchewan hospital guidelines, radionuclide scans for the detection of acute GI bleeding should be performed within the first 24 hours after the test is requested (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). No Canadian benchmarks were found for abdominal angiography wait times. Based on an American guideline, an urgent angiography should be performed within one hour of a positive scintigraphy, regardless of time of the day.[39]

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Although acute LGIB stops without any intervention in 85% of patients, mortality is reported in 2% to 4% of patients.[1,3,13] Higher mortality rates (greater than 5%) have been reported in studies published in the 1980s.[7] Early diagnosis of patients with severe bleeding, and early therapeutic interventions, may lead to lower mortality rates.[13]

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Recurrence can be problematic for patients with LGIB, particularly for ones with chronic GI bleeding, e.g. from diverticulosis or angiodysplasia.[40] Between 5% and 50% of patients with persistent bleeding require surgical interventions.[7] However, advances in diagnostic imaging techniques including nuclear scanning and angiography have changed the management of GI bleeding and resulted in declining rates of recurrence and surgery.[7,40] Our search found no studies investigating the impact of scintigraphic evaluations or visceral angiography on health outcomes or quality of life in patients with LGIB. Chronic LGIB, however, is a significant problem, and failure to diagnose and treat it results in chronic anemia, which does affect quality of life and also can cause anxiety (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert opinion). Two studies were identified by the targeted search that evaluated health-related outcomes following push enteroscopy (endoscopic evaluation of small intestine) in patients with GI bleeding.[41,42] Although push enteroscopy was not a comparator of interest in this review, these two studies were included for review, as it was deemed that push enteroscopy in detection of GI bleeding and guidance of treatment may be similar to that of other modern imaging modalities, including scintigraphy and angiography.

In the study by Vakil et al.,[41] 29 patients with unexplained GI bleeding underwent push enteroscopy. The total number of patients requiring blood transfusion declined significantly in the year following enteroscopy due to appropriate therapeutic interventions, compared with one year preceding the procedure (P = 0.03). Furthermore, in patients who underwent therapeutic interventions at the time of enteroscopy, functional status improved from a Karnofsky performance score of 60 to 90 (P = 0.005).

Hayat et al.[42] studied 21 patients with suspected small intestinal bleeding in the United Kingdom (age range 25 to 87 years) who underwent push enteroscopy to determine the impact of the procedure on the management of GI bleeding and prevention of unnecessary diagnostic testing. Following the test, the certainty of diagnosis increased in 35% of patients, and the mean value of certainty of diagnosis, as perceived by the requesting physicians, increased from 1.35 (prior to the test) to 2.40 (following test, P = 0.01). In 40% of patients, the management and treatment plans changed, based on the results of the test. In addition, the requesting physicians assigned a median “usefulness score” of 3 to the test (on a scale of 1 for “not helpful” to 5 for “very helpful”).

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CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

LGIB is more common in men than in women. Its incidence is also age-dependent, and the annual rate of hospitalization increases from 1 per 100,000 patients in the third decade of life to over 200 per 100,000 patients in the ninth decade. Non-steroidal anti-inflammatory drugs and aspirin are shown to increase the risk of LGIB.

Health disparity might be present if disadvantaged social groups systematically experience poorer health or more health risks than do more advantaged social groups.[43] Disadvantaged groups can be defined based on gender, age, ethnicity, geography, disability, sexual orientation,

socioeconomic status, and special health care needs. Our targeted search found disparity concerns in the following disadvantage groups:

Ethnic and racial groups
GI infections with the bacterium *Helicobacter pylori* are described in Inuit and Alaskan natives; these infections can result in higher rates of iron deficiency anemia due to gastritis or GI bleeding in the Arctic population.

In its 2010 report on health care disparities, the Agency for Healthcare Research and Quality reported the death rates from complications of care, such as sepsis, renal failure, GI bleeding, cardiac arrest and shock, in adult patients admitted to community hospitals in the United States. The indicator is called "failure to rescue." Based on this report, in 2007, the death rates following complications of care — including GI bleeding — were significantly higher in Asians than Whites (130.2 per 1000 compared with 111.3 per 1000).[30] According to the 2009 version of the same report, Hispanics had a higher rate of death due to in-hospital GI bleeding and other complications of care (listed previously) compared to non-Hispanic whites (122.1 per 1,000 compared with 117.1 per 1000).[31]

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

GI Scintigraphy
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

Abdominal angiography
Angiography uses one of three imaging technologies: X-ray, CT, MRI and contrast material to image blood vessels. Patients may have concerns about the injection of contrast media.

Other new techniques, such as CT-angiography (helical CT following injection of a contrast agent) or MR-angiography (MR imaging with an intravascular contrast agent) have also been used to for detection of LGIB.[5,17]

Angiography using CT
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion). Patients may be required to hold their breaths for a substantial period of time, which is seen as "uncomfortable" and "difficult," particularly for patients with severe abdominal pain.[44]

Angiography using MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise; however, this may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension, and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[45,46] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Overall, one systematic review[18] and seven observational studies,[19-25] reported on the diagnostic accuracy of ^{99m}Tc-scintigraphy and angiography. Two qualitative reviews[27,28] were also considered for this review (Appendix 4).

Because our search strategy was designed to identify only studies comparing ^{99m}Tc-scintigraphy to other potential alternatives, the identified studies were mainly focused on the diagnostic accuracy of ^{99m}Tc-scintigraphy (Appendix 4). Angiography was used as the reference of standard in two of the studies.[22,23] The remaining studies used surgical results or a combination of diagnostic procedures (including angiography) and clinical findings as the gold standard. Our search did not capture studies evaluating the diagnostic accuracy of angiography compared to surgery or other references of standards that were used by ^{99m}Tc-scintigraphy studies. Therefore, indirect comparison of ^{99m}Tc-scintigraphy to angiography was not possible. One of the included qualitative reviews summarized the diagnostic accuracy of angiography from nine studies published between 1974 and 1997.[27] No studies comparing the diagnostic accuracy of scintigraphy to CT-angiography or MR-angiography were identified.

Systematic review

A systematic review was undertaken by the Center for Evidence-based Practice of the University of Pennsylvania Health System to inform development of a practice guideline on the management of acute LGIB.[18] This review, published in 2009, included 13 studies measuring the ability of ^{99m}Tc-labelled RBC scintigraphy to localize LGIB compared with other imaging techniques. No details were provided about the methodological quality of the included studies. Reported pooled sensitivity rate was 62% for scintigraphy. The overall percentage of positive test results ranged across the studies from 28% to 65% (pooled rate = 49%). However, according to the authors, the assessment of the diagnostic accuracy of ^{99m}Tc scintigraphy was difficult due to lack of a definitive gold standard in most of the included studies, especially for the patients who had a negative test result. The percentage of the positive scintigraphy results that were confirmed by further diagnostic procedures (e.g., angiography or colonoscopy) or by surgery was reported to range between 41% and 82% (pooled rate = 62%).

Primary studies

No randomized controlled trials evaluating the diagnostic accuracy of the alternative tests of interest were found by the literature search. Seven observational studies,[19-25] including two head-to-head studies of ^{99m}Tc-scintigraphy versus angiography,[22,23] were identified. Six of the eight studies of the included studies compared the accuracy of ^{99m}Tc-scintigraphy with surgery[19,20,24] or a combination of other diagnostic tests (including angiography) and clinical findings[20,21,25] (Appendix 4). The scintigraphic techniques varied across the included studies.

Peynircioglu et al.[23] retrospectively studied 45 patients with massive GI bleeding (requiring more than four units of blood in 24 hours and systolic blood pressure less than 90 mmHg) who were referred to receive transcatheter mesenteric angiography. All of the patients had previous endoscopy, scintigraphy, or CT angiography (CTA). Sensitivity and specificity of scintigraphy was calculated for the patients who underwent scintigraphy prior to angiography (18 patients with LGIB and four patients with lower and upper GI bleeding). The results are shown in Appendix 4. In this study, the diagnostic accuracy of endoscopy and CTA was also compared with angiography. Based on their study findings, the authors concluded that scintigraphy should be performed to detect LGIB prior to angiography. They also stressed that CTA should be considered as an alternative to scintigraphy in emergency settings, due to its ability to provide broader insight into the underlying causes of LGIB.

Brunnler et al.[22] retrospectively evaluated the results of scintigraphy in 92 patients with suspected obscure GI bleeding. However, the diagnostic accuracy of scintigraphy was reported based on the results of the test in 33 patients who underwent angiography, as well. Compared with angiography, as the gold standard, scintigraphy had an overall sensitivity of 79% and a specificity of 30% in the detection of LGIB. The safety outcomes were also recorded in this study. The authors concluded that scintigraphy studies were safe and superior to angiography. They concluded that scintigraphy could be a helpful procedure, particularly for older patients in whom invasive procedures are of concern.

Howarth et al.[21] reported the diagnostic ability of scintigraphic studies in correct localization of obscure GI bleeding in a series of 137 hospitalized patients. All of the patients underwent ^{99m}Tc-labelled RBC scintigraphy. Some patients underwent additional diagnostic tests, such as colonoscopy or angiography. However, the final diagnoses were made using hospital discharge diagnosis or clinical confirmation of definite GI bleeding (e.g., rectal blood loss and/or hypovolemic shock). In this study, scintigraphy showed a sensitivity of 87% in the detection of active bleeding and 54% in the localization of GI bleeding. The results of the study also showed that the diagnostic ability of ^{99m}Tc-labelled RBC scintigraphy in localizing active bleeding is significantly lower in the small intestine than in the colon. The authors concluded that, in most cases, detection and localization of GI bleeding may require more than one diagnostic test, and that the diagnostic accuracy of endoscopic and angiographic investigations are lower than scintigraphy in cases of intermittent GI bleeding.

Wu et al.[20] evaluated the clinical value of two ^{99m}Tc-labelled scintigraphy techniques in 90 patients referred with clinical evidence of GI bleeding: conventional non-subtraction scintigraphy (CNS), and sequential subtraction scintigraphy (SSS). All patients underwent 12 CNS imaging every five minutes, up to 60 minutes. Then, 11 SSS images were obtained with “t+5” minutes subtracted from each other (using a computer), up to 60 minutes. Delayed images were obtained until 24 hours if the early images were non-diagnostic. The results of each scintigraphy technique were compared to the final diagnoses made by endoscopy, angiography, surgery, and clinical findings. The sensitivity of scintigraphic images taken at 30 minutes was 56.4% and 87% for CNS and SSS, respectively. Images taken at 60 minutes yielded a sensitivity of 85.4 % and 91.9% for CNS and SSS, respectively. In 62 patients who underwent surgical operation, the sensitivity of scintigraphic techniques in localization of the bleeding site was also compared to the surgical findings (92.8% and 73.8% for CNS and SSS, respectively) (Appendix 4). The authors concluded that SSS can be considered as a suitable technique in pediatrics, the elderly, and critically ill patients due to its higher sensitivity and shorter examination time.

O’Neill et al.[24] performed a retrospective chart review of a series or 26 patients with upper and lower GI bleeding who underwent cinematic ^{99m}Tc-labelled RBC scintigraphy. Twenty-five of 26 patients also underwent surgical operation, and the results of surgery were considered as the gold standard. The site of bleeding was correctly localized by scintigraphy in 88% of patients. Eleven patients (42%) also underwent angiography, in which four examinations were documented as negative. Three of four patients with negative angiograms had a positive scintigraphy. However, the final diagnoses of these cases, made following surgery, were not mentioned in the article. The authors concluded that cinematic ^{99m}Tc-labelled RBC scintigraphy is a sensitive and non-invasive alternative to angiography in localizing the site of GI bleedings.

Emslie et al.[25] reviewed the medical records of 80 patients who underwent ^{99m}Tc-labelled RBC scintigraphy for diagnosis of GI bleeding in a single centre. The results were compared with confirmatory studies, such as angiography, colonoscopy, surgery, or combinations of them.

Overall, the results of scintigraphy were concordant with the final diagnosis in 60 of 75 patients (accuracy = 80%). Scintigraphy was reported to have a sensitivity of 88%. Based on their results, the authors recommended ^{99m}Tc-labelled RBC scintigraphy as a non-invasive, quick, and easily performed test that can be considered as an initial test for the diagnosis of GI bleeding.

Gutierrez et al.[19] retrospectively studied the medical records of 105 patients who had a ^{99m}Tc-labelled RBC scintigraphy for the diagnosis of LGIB. Ninety per cent of the patients had additional diagnostic procedures. Twenty-five of 105 patients underwent surgical operations. Surgical evidence was used as the reference standard in this group to show that scintigraphy correctly identified the site of bleeding in 22 patients (accuracy = 88%). The authors concluded that ^{99m}Tc-labelled RBC scintigraphy should be used as the primary diagnostic test, early in the hospital course. They emphasized that scintigraphy can improve patient outcomes by guiding the surgeon in segmental resection of the affected site.

Qualitative literature reviews
Two of the primary studies[24,25] provided a qualitative summary of the results of other observational studies on the accuracy of scintigraphy in the diagnosis of GI bleeding, as background information in their articles. Two additional qualitative reviews[27,28] summarized the results of case-series and observational studies to demonstrate the ability of scintigraphy detection and localization of LGIB. One of these reviews[27] also included the findings of nine studies evaluating the accuracy of abdominal angiography in the diagnosis of LGIB. The results are shown in Appendix 4.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

^{99m}Tc-scintigraphy for GI bleeding
^{99m}Tc-scintigraphy is non-invasive and associated with no morbidities[2] or mortalities.[22] On rare occasions, allergic reactions to radiopharmaceuticals used for scintigraphy may occur.[12,32]

Abdominal Angiography
Angiography is an invasive procedure with a potential for major complications, particularly in the elderly and in patients with comorbid illness.[12,28] Adverse events (AEs) are reported in 0% to 26% of patients undergoing angiography.[2,7,28] The most common complication is hematoma or bleeding at the catheter site.[7] Other potential AEs include arterial dissection, catheter site infection, loss of pulses in lower extremity, and contrast reaction.[2,7,12,28]

Other new techniques, such as CT-angiography (helical CT following injection of contrast agent) or MR-angiography (MRI with an intravascular contrast agent), have also been used to detect LGIB.[5,17]

Angiography using CT
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[47] In addition, patients may experience mild side effects from the contrast agent such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium (Gd) contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found that 0.15% of

patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[48] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. According to the American College of Radiology *Manual on Contrast Media*,[49] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[49]

Angiography using MRI

MRI is contraindicated in patients with metallic implants including pacemakers.[50] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[47] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[49] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[49]

Radiation-related Risks

Among the modalities to diagnose lower gastrointestinal bleeding, both GI bleeding scintigraphy and angiography expose the patient to ionizing radiation. The average effective dose of radiation delivered can be found in Table 2. As the table shows, abdominal angiography delivers larger doses of radiation than GI scintigraphy. A precise comparison of radiation doses used by the two diagnostic tests is difficult because a part of radiation exposure from angiography is related to the therapeutic component of this procedure.[2]

Table 2: Effective Doses of Radiation

Procedure	Average Effective Dose (mSv)
GI scintigraphy	7.8[33]
Abdominal angiography	12[33]
Average background dose of radiation per year	1 to 3.0[34-36]

GI = gastrointestinal; mSv = millisevert.

Return to Summary Table.

CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to diagnose lower GI bleeding are presented by imaging modality. A summary of the availability of personnel required for the conduct of methods to diagnose lower GI bleeding, by GI scintigraphy or any of the alternative imaging modalities, is provided in Tables 3 and 4.

GI Scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of GI scintigraphy should be nuclear medicine physicians or diagnostic radiologists with training and expertise in nuclear imaging.[51] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct GI scintigraphy. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

Abdominal Angiography
To perform abdominal angiography, diagnostic radiologists should be qualified in vascular/interventional radiology[32] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists are also qualified if they are certified by a recognized certifying body and hold a valid provincial licence.[51]

Table 3: Medical Imaging and GI Professionals in Canada in 2006[32,52,53]

Professional	Total Number of Professionals in Canada	Provinces and Territories with no professionals available
Diagnostic radiology physicians	2,034	YT, NT, NU
Nuclear medicine physicians	221	PEI, YT, NT, NU
Medical physicists	322	PEI, YT, NT, NU
Gastroenterologists	525	NA
Radiological technologists	12,255	Available in all jurisdictions
Nuclear medicine technologists	1,781	1 technologist for all territories

NA = not available; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; YT = Yukon.

Table 4: Medical Imaging Professionals in Canada[32]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	Medical Radiation Technologists	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR

Table 4: Medical Imaging Professionals in Canada[32]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**Medical Radiation Technologists**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; ON = Ontario; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jusrisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 5 provides an overview of the availability of equipment required to diagnose lower GI bleeding.

Table 5: Diagnostic Imaging Equipment in Canada[32,54]			
	Nuclear Medicine Cameras	**Angiography Suites**	**SPECT/CT Scanners**
Number of devices	603[32]	179[32]	96[54]
Average number of hours of operation per week (2006–2007)[32]	39	40	n/a
Provinces and territories with no devices available	YT, NT, NU	YT, NT, NU	PEI, YT, NT, NU

CAR = Canadian Association of Radiologists; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; SPECT/CT = single-photon emission computed tomography/computed tomography;YT = Yukon.

GI scintigraphy

To perform GI scintigraphy, nuclear medicine facilities with gamma cameras are required. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[32] ^{99m}Tc-labelled RBC scintigraphy is usually used for detection and localization of intermittent bleeding, in which episodes of bleeding may only occur for short periods of time. Thus, the likelihood of a positive diagnosis depends on repeated, and sometimes continuous, image acquisition. Therefore, limitations of equipment and imaging time may affect the sensitivity of this technique in the diagnosis of LGIB.[9]

In 2007, the latest year for which data are available, the average time for nuclear medicine examinations at McGill University Health Centre hospitals was five days. However, the wait times were reported to be less than one day for emergency cases.[38] In the same year, wait times of angiography procedures at McGill University Health Centre hospitals were 21 days in general, and less than 12 hours for emergency and urgent cases.[38]

Abdominal angiography
Abdominal angiography should be performed in an angiography suite equipped to a minimum of a high-resolution image intensifier, and television chain with standard angiographic filming capabilities and adequate angiographic supplies. Digital angiographic systems are also recommended. Appropriate emergency equipment and medications must be immediately available to treat AEs associated with administered medications. The equipment, medications, and other emergency support must also be appropriate for the range of ages and sizes in the patient population.[37]

Return to Summary Table.

CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of ^{99m}Tc-labelled RBC scintigraphy and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 6), the cost of ^{99m}Tc-labelled RBC scintigraphy is $239.80. Abdominal angiography is a significantly more costly alternative.

Table 6: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[55]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
^{99m}Tc-labelled RBC scintigraphy				
J878	Abdominal scintigraphy — for gastrointestinal bleed-labelled RBCs	146.85	50.95	197.80
Maintenance fees — from global budget		42.00		42.00
	TOTAL	188.85	50.95	**239.80**
Abdominal angiography				
X181B X181C	Abdominal, thoracic, cervical, or cranial angiogram by catheterization using film changer, cine, or multiformat camera — non-selective	61.20	32.50	93.70
X182B X182C (×3)	Abdominal, thoracic, cervical, or cranial angiogram by catheterization using film changer, cine, or multiformat camera — selective (per vessel, to a maximum of 4)	81.35 (×3) = 244.05	39.40 (×3) = 118.20	362.25
J021	Insertion of catheter (including cut-down, if		121.40	211.46

Table 6: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[55]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
	necessary) and injection, if given		(Spec) 90.06 (Anes)	
J022 (×3)	Selective catheterization — add to catheter insertion fee (per vessel, to maximum of 4), each 60.15		60.15 (×3) = 180.45	180.45
	Maintenance fees — from global budget	51.00		51.00
	TOTAL	356.25	542.61	**898.86**

Prof. = professional; RBC = red blood cells; ^{99m}Tc = technetium-99m; Tech. =technical.

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APPENDIX

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
	to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1948 to March 1, 2011>
Date of Search:	March 2, 2011
Alerts:	Monthly search updates began March 1, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	No date limit for systematic reviews; publication years 1996 – March 2011 for primary studies English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Ovid MEDLINE Strategy	
Line #	**Search Strategy**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	radioisotope*.mp.
6	(technetium* or TC-99* or TC99* or TC-99m* or TC99m* or 99mTC* or 99m-

Ovid MEDLINE Strategy	
	TC* or 99mtechnetium* or 99m-technetium* or TC-rhenium-sulfur aerosol or TCReS colloid).tw,nm.
7	Radionuclide Imaging/ or Perfusion Imaging/
8	Tomography, Emission-Computed, Single-Photon/
9	ri.fs.
10	(((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)) or scintigraph* or scintigram* or scintiphotograph*).tw.
11	(single-photon adj2 emission*).tw.
12	(RBC adj5 (imaging or scan*)).tw.
13	(red adj2 cell* adj5 (imaging or scan*)).tw.
14	(sulfur colloid* adj5 (imaging or scan*)).tw.
15	or/1-14
16	Gastrointestinal Hemorrhage/
17	((GI or gastric or gastrointestin* or gastro-intestin* or nonvariceal* or non-variceal*) adj5 (bleed* or blood or hemorrhage* or haemorrhage* or lesion or rebleed*)).tw.
18	(hematochezia* or LGIB).tw.
19	or/16-18
20	Meta-Analysis.pt.
21	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
23	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
25	(data synthes* or data extraction* or data abstraction*).tw.
26	(handsearch* or hand search*).tw.
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.
28	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).tw.
29	(meta regression* or metaregression* or mega regression*).tw.
30	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
31	(medline or Cochrane or pubmed or medlars).tw,hw.
32	(cochrane or health technology assessment or evidence report).jw.
33	or/20-32

Ovid MEDLINE Strategy	
34	exp "Sensitivity and Specificity"/
35	False Positive Reactions/
36	False Negative Reactions/
37	du.fs.
38	sensitivit*.tw.
39	(predictive adj4 value*).tw.
40	distinguish*.tw.
41	differentiat*.tw.
42	enhancement.tw.
43	identif*.tw.
44	detect*.tw.
45	diagnos*.tw.
46	accura*.tw.
47	comparison*.tw.
48	Comparative Study.pt.
49	(Validation Studies or Evaluation Studies).pt.
50	Randomized Controlled Trial.pt.
51	Controlled Clinical Trial.pt.
52	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
53	Multicenter Study.pt.
54	(random* or sham or placebo*).ti.
55	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
56	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
57	(control* adj3 (study or studies or trial*)).ti.
58	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
59	(allocated adj "to").ti.
60	Cohort Studies/
61	Longitudinal Studies/
62	Prospective Studies/
63	Follow-Up Studies/
64	Retrospective Studies/
65	Case-Control Studies/
66	Cross-Sectional Study/
67	(observational adj3 (study or studies or design or analysis or analyses)).ti.
68	cohort.ti.
69	(prospective adj7 (study or studies or design or analysis or analyses or

Ovid MEDLINE Strategy	
	cohort)).ti.
70	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
71	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
72	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
73	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
74	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
75	(population adj3 (study or studies or analysis or analyses)).ti.
76	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
77	or/34-76
78	Case Reports.pt.
79	77 not 78
80	15 and 19 and 33
81	limit 80 to english language
82	15 and 19 and 79
83	limit 82 to (english language and humans and yr="1996 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 1, 2011	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCHING	
Dates for Search:	March 2011
Keywords:	Included terms for radionuclide imaging and gastrointestinal hemorrhage.
Limits:	No limits

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

Appendix 3: Definitions

Angiodysplasia: A small vascular malformation of the intestine. It is a common cause of unexplained gastrointestinal bleeding and anemia.

Extravasation: Extravasation refers to a discharge or escape of blood from a vessel into the tissues.

Meckel's diverticulum: A Meckel's diverticulum is a pouch on the wall of the lower part of the intestine that is present at birth and may contain tissue that is identical to tissue of the stomach or pancreas.

Millisievert (mSv): The sievert, named after Rolf Sievert, a Swedish medical physicist, is a unit of dose equivalent. It shows the biological effects of radiation as opposed to the physical aspects, which are characterized by the absorbed dose (milligray). mSv is one-thousandth of sievert.

The Karnofsky Performance Status: An instrument that was originally designed as a measure of functional performance to be used in evaluating the efficacy of cancer chemotherapy trials. It is currently used as a measure given by a patient's physician to assess the patient's ability to perform certain ordinary tasks. The lower the Karnofsky score, the worse the survival for most serious illnesses. The general categories are as follows: score 80 to100 — able to carry out normal activity, no special care needed, may need assistance to care for needs; score 40 to 70 — unable to work, able to live at home and care for most personal needs; score 10 to 40 — unable to care for self, requires institutional care or equivalent.

Visual Analog Scale (VAS): A VAS usually consists of a single horizontal line on a page, with verbal and numerical descriptors at each end. Vertical lines and sometimes numbers are added to make scale units. One end point of the line (usually denoted as 10 or 100) is labelled as "the best health state possible" and the opposite end point (denoted as 0) is labelled as "the worst health state possible."

Appendix 4: Diagnostic Accuracy

Table 8 : Accuracy of ^{99m}TC scan in Diagnosis of Lower Gastrointestinal Bleeding								
Study	**Country**	**Study Design (data collection period)**	**Inclusion Criteria (no. of patients)**	**Standard of Reference**	**Test**	**Diagnostic Accuracy**		
						Sensitivity %	**Specificity %**	**Other**
Peynircioglu et al., 2011[23]	Turkey	Retrospective case series (4 years)	Massive GI bleeding (22)	Angiography	^{99m}Tc scan	50	66.7	PPV: 42.9% NPV: 72.7% (prevalence: 39%*)
Brunnler et al., 2008[22]	Germany	Retrospective medical record review (7 years)	Obscure GI bleeding (92)	Angiography	^{99m}Tc scan	79	30	PPV: 77% NPV: 76% (prevalence: 33%*)
Howarth et al., 2002[21]	Australia	Retrospective case series (5 year)	Obscure GI bleeding (47)	Clinical discharge diagnosis or clinical confirmation of GI bleeding	^{99m}Tc-RBC scan	87 (detection) 54 (localization)	–	–
Wu & Seto, 2001[20]	China	Retrospective case series (NA)	GI bleeding (90)	Endoscopy, angiography, and clinical findings	Non-subtraction ^{99m}Tc-RBC scan	56.4 (30-min. image) 85.4 (60-min. image)	–	–
					sequential subtraction ^{99m}Tc-RBC scan	87 (30-min. image) 91.9 (60-min. image)	–	–
				Surgery (62 patients)	Non-subtraction ^{99m}Tc-RBC scan	92.8	–	–
					Sequential subtraction ^{99m}Tc-RBC scan	73.8	–	–

Table 8 : Accuracy of ^{99m}TC scan in Diagnosis of Lower Gastrointestinal Bleeding								
Study	**Country**	**Study Design (data collection period)**	**Inclusion Criteria (no. of patients)**	**Standard of Reference**	**Test**	**Diagnostic Accuracy**		
						Sensitivity %	**Specificity %**	**Other**
O'Neill et al., 2000[24]	USA	Retrospective medical record review (7 years)	Upper and lower GI bleeding who underwent cinematic TC-99m RBC scans and required surgical intervention (26)	Surgery (intraoperative findings, surgical pathology, post-operative clinical course)	^{99m}Tc-RBC scan	88	–	–
Emslie et al., 1996[25]	USA	Retrospective case series (4 years)	Lower GI bleeding (80)	Confirmatory studies (angiography, colonoscopy, surgery)	^{99m}Tc-RBC scan	88*	85*	Accuracy 80%*
Gutierrez et al., 1998[19]	USA	Retrospective medical record review (4 years)	Lower GI bleeding (105)	Surgery	^{99m}Tc-RBC scan	88	–	–

GI = gastrointestinal; ^{99m}Tc = technetium-99m; RBC = red blood cell; min. = minute; PPV = positive predictive value; NPV = negative predictive value; NA = not available.
*Calculated using data from article.

Table 9: Rates of correct localization of LGIB by ^{99m}Tc scintigraphy or angiography, reported by qualitative reviews				
Review	**Test**	**No of included studies (total number of tested patients)**	**Correct localization of LGIB %**	
			Range (reported by included studies)	**Summary estimate**
Hoedema, 2005[27]	^{99m}Tc scan	8 (380)	52 to 95	NA
	Angiography	9 (436)	40 to 86	NA
Strate, 2010[28]	^{99m}Tc scan	7 (447)	44 to 100	68

LGIB = lower gastrointestinal bleeding; NA = not available; ^{99m}Tc= technetium 99m

APPENDIX 2.2

INDICATION OVERVIEW

Perforation or blockage of the bile duct can occur after surgeries such as laparoscopic cholecystectomy or liver transplant, or could happen following trauma.[1] A retrospective and prospective study[2] of Canadian patients with biliary leaks post cholecystectomy reported the frequency of the symptoms that patients with leak experienced, as follows: abdominal pain (89%), fever (43%), abdominal tenderness (81%), jaundice (43%), nausea and vomiting (43%), and ascites or mass (2%).

Population: Adults and children with suspected bile leak.

Intervention: Cholescintigraphy (also known as hepatobiliary scintigraphy [HBS] or hepatobiliary iminodiacetic acid [HIDA] scan).

Nuclear imaging is used to visualize the perforations or blockages. The isotope attaches to liver cells (hepatocytes) and is excreted in bile.[3] The imaging will detect bile in areas where it should not be, indicative of a leak, or will show a lack of bile in areas where it should be (such as the gall bladder), indicative of an obstruction.

The radioisotopes used for the cholescintigraphy are all iminodiacetic acid derivatives and include mebrofenin, disofenin, and diisopropyl.

Comparators: For this report, the following diagnostic tests are considered as alternatives to cholescintigraphy:

- *Computed Tomography (CT):* In a CT scan, a rotating x-ray device moves around the patient and takes detailed multiple images of organs and body parts.[4] Sometimes patients are injected with a contrast dye before images are taken, for better visualization of the body part being examined.[4] CT findings consistent with bile leak include the presence of fluid collections in the gallbladder fossa.[5]
- *Endoscopic Retrograde Cholangiopancreatography (ERCP):* An ERCP is a test using an endoscope and x-rays to examine a patient's bile and pancreatic ducts.[6] During the ERCP, an endoscope is placed in the patient's mouth and passed through the esophagus, stomach, and intestine. The endoscope is a long, flexible tube that contains a lens and a light source that allows for viewing inside the body. Patients are given sedation and need to fast six to eight hours prior to the examination.[7]
- *Magnetic Resonance Cholangiopancreatography (MRCP):* An MRCP is a magnetic resonance imaging (MRI) test that produces detailed images of the hepatobiliary and pancreatic systems. Images are created using a magnetic field and radiofrequency pulses. Patients undergoing MRI are placed onto a table that is moved into the centre of the MRI machine. Some patients are given contrast material before the MRI. MRCP findings indicative of bile leak include the presence of fluid near the perforation site and related bile duct anomalies.[8]

- *Ultrasound (U/S):* During a U/S, a transducer is placed over the organ of interest. The transducer generates sound waves that pass through the body and produce echoes, which are analyzed by a computer to produce images of the body part being analyzed.[9] In the detection of bile leak, U/S can detect fluid collections that could be indicative of bile leak in the abdomen and hepatic system.[5,10]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and biliary leak.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials, non-randomized studies, and diagnostic accuracy studies. No date or human limits were applied to the HTA/SR/MA search. For primary studies, no date limit was applied, but the search was limited to the human population. Both searches were also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

Two potential clinical articles were identified through the MA/SR/HTA filtered search and neither was subjected to full text review. A total of 511 primary studies were identified with the primary studies search, of which 96 were subjected to full-text screening.

Fourteen articles were retained that provided information for the following criteria: affected population;[2,11,12] urgency;[13] morbidity and quality of life;[13-15] acceptability of the test to patients;[16,17] diagnostic accuracy;[5,10,18-20] risks;[16] and availability.[16] The remaining 43 citations were articles found through searching the grey literature, articles from the targeted searches, or articles from the reference lists of the identified potential articles.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	The number of liver transplantations in Canada has been increasing over the last decade, with 409 transplants performed in 2000 and 452 performed in 2009. Of these transplants, 65% were done in males.[21] The average (SD) annual liver resection rate in Ontario in 2001 was 5.90 (4.0) per 100,000 people.[22] The overall annual rate (95% confidence interval [CI]) of elective cholecystectomy in Ontario, from 1988 to 2000, was 134.6 (133.6 to 135.6) per 100,000 people for men and 367.5 (365.9 to 369.1) per 100,000 people for women.[23] Incidence of bile leak ranged from 2% to 17% in patients undergoing liver transplantation, hepatectomy, or cholecystectomy. Based on the available estimates, the size of affected population may be more than 1 in 10,000 (0.01%) and less than or equal to 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	Imaging should take place immediately to 24 hours after onset of symptoms post-surgery. No information regarding urgency was identified. The target time frame for performing the test is in 24 hours or less and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has moderate impact on the management of the condition or the effective use of health care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	Reported in-hospital mortality rates due to bile leak vary from 7.8% to 8.8%, with 30-day mortality reported to be 2.6%. Late mortality rate (after 30 days) is reported to be 5.9%.[24] Diagnostic imaging test results can have moderate impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Symptoms from bile leaks may persist for months. Sepsis, peritonitis, and liver failure are serious events associated with bile leak. These serious events have significant morbidity associated with them. Leaks may require surgical repair, which increases morbidity, mortality, and length of hospital stay in both adult and pediatric populations. Bile leak can manifest clinically after a latent period[15] following blunt trauma in children. A delay in the detection of bile duct injury may result in increased morbidity, and prolonged hospitalization. Diagnostic imaging test results can have significant impact on morbidity or quality of life.

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	*Cholescintigraphy* Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. *CT* Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion). Patients may be required to hold their breath for a substantial period of time, which is seen as "uncomfortable" and "difficult," particularly for patients with severe abdominal pain.[25] *ERCP* ERCP is a relatively invasive test. It involves inserting an endoscope through the patient's mouth, and down the esophagus until it reaches the duodenum. *MRCP* MRCP is an MRI-based imaging test. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[26,27] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.When compared, ERCP was found to be an easier test relative to expectations than MRCP, and patients reported a higher preference for MRCP than ERCP.[28] *U/S* Some discomforts associated with U/S include cold, unspecified pain, and tenderness. In a study comparing U/S with MRI in undiagnosed shoulder pain, 100% of the patients participating said that they would be willing to undergo the U/S exam again.[29] This test may be preferred in pediatric patients as there is no exposure to ionizing radiation, and the test does not require sedation. Overall, the acceptability to the patient of cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is: • minimally more acceptable than CT • significantly more acceptable than ERCP

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		• minimally less acceptable than MRCP • minimally less acceptable than U/S.
7	**Relative diagnostic accuracy of the test**	Diagnostic accuracy studies all had relatively small sample sizes, and the reported sensitivity, specificity, and detection rates varied considerably. See Appendix 4. While all modalities can identify fluid collection, only cholescintigraphy and MRCP can identify the fluid as bile. Therefore, MRCP may be the most suitable alternative to cholescintigraphy. Overall, the diagnostic accuracy of cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is: • moderately better than CT • moderately lower than ERCP • similar to MRCP • moderately better than U/S.
8	**Relative risks associated with the test**	**Non–radiation-related risks** *Cholescintigraphy* Risks associated with cholescintigraphy include allergy to HIDA and pain during CCK injection (causes gallbladder contraction), chills, nausea, and rash.[30] *CT* Some patients may experience an allergic reaction to the contrast agent (if required).[31] In addition, patients may experience mild side effects from the contrast agent, such as nausea, vomiting, or hives. *ERCP* ERCP is an invasive endoscopy-based procedure and can lead to further complications.[32] Prolonged cannulation may cause additional morbidity to patients and unnecessary radiation exposure.[33] ERCP is also associated with a morbidity rate (15.8%). Morbidity-related complications may include pancreatitis, hemorrhage, perforation, cholangitis, perforated stent, and complications related to cardiac, respiratory, and thromboembolic systems.[34] *MRCP* MRCP is an MRI-based exam. MRI is contraindicated in patients with metallic implants including pacemakers.[35] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required).[31] Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis.

<table>
<tr><th colspan="3">**Table 1:** Summary of Criterion Evidence</th></tr>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>Contrast-related reactions are similar to those experienced with CT.

U/S
There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks
Cholescintigraphy, CT, and ERCP are associated with radiation exposure.

<table>
<tr><th colspan="3">Effective Radiation Doses</th></tr>
<tr><th>Test</th><th>Effective Radiation Dose (mSv)</th><th>Pediatric Effective Dose Estimate Range (mSv)</th></tr>
<tr><td>Cholescintigraphy using ^{99m}Tc-disofenin or ^{99m}Tc-mebrofenin</td><td>3.1[36]</td><td>NR</td></tr>
<tr><td>CT</td><td>8.0[37]</td><td>8.0[37]</td></tr>
<tr><td>ERCP*</td><td>1 to 10[38]</td><td>0.3 to 3[38]</td></tr>
<tr><td>MRCP (MRI)</td><td>0</td><td>0</td></tr>
<tr><td>U/S</td><td>0</td><td>0</td></tr>
<tr><td>Average background dose of radiation per year</td><td>1 to 3.0[37,39,40]</td><td>1 to 3.0[37,39,40]</td></tr>
</table>
CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; mSv = millisievert; ^{99m}Tc = technetium-99m; U/S = ultrasound.

Overall, the safety of cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is:
• minimally safer than CT
• significantly safer than ERCP
• minimally less safe than MRCP
• minimally less safe than U/S.</td></tr>
<tr><td>9</td><td>Relative availability of personnel with expertise and</td><td>As of 2006 in Canada, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, 1,781 nuclear medicine technologists, and 2,900 sonographers available across Canada. Yukon, Northwest Territories, and Nunavut do not have the available</td></tr>
</table>

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
	experience required for the test	personnel to perform and interpret tests to detect bile leak. Other jurisdictions (e.g., Prince Edward Island) may offer limited nuclear medicine services. Gastroenterologists or those physicians trained in endoscopic procedures may be restricted to larger centres. Assuming the necessary equipment is available, if cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using CT • fewer than 25% of the procedures can be performed in a timely manner using ERCP, • 25-74% of the procedures can be performed in a timely manner using MRCP • more than 95% of the procedures can be performed in a timely manner using U/S.
10	**Accessibility of alternative tests (equipment and wait times)**	*Cholescintigraphy* For detection of bile leak, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[41] *ERCP* ERCP is an x-ray–based test. X-ray machines are widely available across the country. *MRCP* No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[42] According to the CIHI National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006-2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario with a national average of 71 hours.[41] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[43] *CT* No CT scanners are available in Nunavut.[42] For CT scanners, the average weekly use ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[41] *U/S* The median wait time for a U/S in Canada was estimated to be 4.5 weeks in 2010.[43] No information was found on the number of U/S machines available in Canada.[41] Assuming the necessary expertise is available, if cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that: • 95% of the procedures can be performed in a timely manner using CT

Table 1: Summary of Criterion Evidence

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses

Criterion		Synthesized Information
		• 25-74% of the procedures can be performed in a timely manner using ERCP • 25-74% of the procedure can be performed in a timely manner using MRCP, • 95% of the procedures can be performed in a timely manner using U/S.
11	**Relative cost of the test**	According to our estimates, the cost of cholescintigraphy with ^{99m}Tc-based radioisotopes is $247.85. CT is minimally more costly, MRCP is moderately more costly, and ERCP is significantly more costly. Imaging using U/S is less costly than scintigraphy.

Relative costs

Test	Total costs ($)	Cost of test relative to ^{99m}Tc-based test ($)
Cholescintigraphy	247.85	Reference
CT	383.85	+136.00
ERCP	1900.00	+1652.15
MRCP	652.00	+404.15
U/S	88.25	-159.60

CCK = cholecystokinin; CI = confidence interval; CIHI = Canadian Institute for Health Information; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; Gd = gadolinium; HIDA = hepatobiliary iminodiacetic acid; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; MRT = medical radiation technologist; NA = not available; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99; U/S = ultrasound.

CRITERION 1: Size of affected population (link to definition)

Bile leaks may occur after liver transplantation, hepatectomy (liver resection), trauma, or cholecystectomy. The number of liver transplantations in Canada has been increasing over the last decade, with 409 transplants performed in 2000 and 452 performed in 2009. Of these transplants, 65% were done in males.[21] The average (SD) annual liver resection rate in Ontario in 2001 was 5.90 (4.0) per 100,000 people.[22]

The overall annual rate (95% confidence interval [CI]) of elective cholecystectomy (gallbladder removal) in Ontario, from 1988 to 2000, was 134.6 (133.6 to 135.6) per 100,000 people for men and 367.5 (365.9 to 369.1) per 100,000 people for women.[23]

A systematic review[44] included 55 articles reporting on biliary complications related to biliary reconstruction during liver transplantation. The authors give no details on the quality of these articles except to state that no articles published before 1990 were included. There were 11,397 cases and 936 were complicated with biliary leakage with a mean incidence of 8.2%. The mean incidence was lower for deceased-donor whole liver transplants (7.8%, 668/8,585) and higher for living-donor transplants (9.5% 268/2,812). Incidence of bile leak for liver donors is reported to be 2% to 5% from institutional data from Tucker and Heaton.[45]

In a study conducted by Vigano et al., post-operative leak occurred in 5.7% of patients (34/593) who had undergone a hepatectomy.[46] Vigano et al. also reported that over the past decade, the incidence of bile leak ranged from 1.7% to 9.2%, and within a cohort of 610 consecutive hepatic resections, the incidence of bile leak was 3.6%.[46] A retrospective study of 616 patients undergoing hepatectomy from January 1989-1998 had an incidence of bile leak of 5.5%.[12] In cases of liver resection, bile leaks occur at a rate ranging from 3.6% to 17%.[47]

The prognosis after a bile leak varies according to the site of the leak and the etiology.[24] Leaks are more common with duct-enteric anastomosis than duct-duct anastomosis.[24]

A prospective study of 71 patients undergoing laparoscopic cholecystectomy reported an incidence of 11.3% of bile leaks.[11] Sixty-four patients evaluated over a five-year period in a study conducted by Barkun et al. reported an incidence rate of 1.1% in patients post laparoscopic cholecystectomy.[2]

Return to Summary Table

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

The priority for cholescintigraphy in diagnosing suspected post-operative biliary leak is stat to 24 hours after symptom onset, according to the Saskatchewan Ministry of Health (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). Delays in diagnosis and therapy frequently result in sepsis and death.[24]

Surgical repair for an ongoing bile leak may compromise the patient, as the bile may be toxic and contribute to additional infection that could lead to poor surgical healing; therefore, some argue that early detection is best treated with drainage.[13]

A study evaluating spontaneous healing of bile leaks examined the correlation between the delay of bile leakage post-operation and interventional treatment. Of 34 patients, leaks in 26

patients healed spontaneously (76.5%), and the conservative treatment failed in eight patients (23.5%). The authors concluded that a “wait and see” approach, compared with interventional treatment (after diagnosis), is successful in most cases.[46] Delayed repair of injured biliary tracts is recommended instead of immediate repair.[45]

Return to Summary Table

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

It has been reported that 44% of patients with bile duct leaks may develop a serious post-operative complication, which could include peritonitis, sepsis, abscess, pulmonary infiltrates, and death.[48] A 30-day mortality rate of 2.6% has been reported, as well as a 7.8% in-hospital mortality rate.[48] Sepsis, leading to multisystem organ failure, is the most common cause of death.[48]

Similar mortality rates were reported by Vigano et al.[46] from a study of patients with post-operative bile leakage. Two of 34 patients (5.9%) with post-operative bile leakage died. One patient died of sepsis with persistent bile leakage 46 days after onset, and the second patient experienced tumour progression with persistent bile leakage and died five months after onset.

Return to Summary Table

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

In a series of case reports presented by Tucker et al., morbidity associated with bile leak included jaundice, abdominal pain, leukocytosis, fever, and shoulder pain.[45]

The presence of bile and blood in the peritoneal cavity due to leakage may impair the host immune system and allow for the development of sepsis, liver failure, and mortality.[12] Bile leak from the parenchymal cut surface can lead to the development of biloma and intra-abdominal infection with abscess.[45]

Vigano et al.[46] evaluated a post-operative bile leakage population of 34 patients with a mean age of 62 years. Although 76.5% patients experienced spontaneous healing after 15 days of the procedure, eight patients did not. Five patients (14.7%) developed associated morbidity accompanying leakage and three patients developed significant morbidity (8.82%), which included sepsis in two and bile peritonitis in one.[46]

Persistent bile leak or drainage can lead to invasive treatment such as ERCP, sphincterotomy, and stent placement. These procedures assist in defining the location of the leak and assist with enteric biliary damage and leak closure. Nasobiliary tubes may also be used to decompress the bile duct and resolve the bile leak.[45,47] Although leaks do heal over time with such interventions, they may persist for months.[47] In some cases, surgical repair or biliary reconstruction, including revising the Roux-en-Y hepaticojejunostomy, creating a new hepaticojejunostomy, or reinforcing the anastomosis with polydioxanone suture (PDS).[13]

One study[14] that followed 40 patients hospitalized after trauma reported statistically significantly ($P < 0.0001$) longer hospital stays for patients who experienced bile leaks compared with those who did not have bile leaks. The mean (SD) length of hospital stay was 53 days (24 days; range

26 to 70 days) for bile leaks compared with a mean of 14 days (12 days; range three days to 61 days) for patients with no bile leaks.

Pediatric
Bile leak can manifest clinically after a latent period[15] following blunt trauma in children. A delay in the diagnosis of bile duct injury may result in increased morbidity and prolonged hospitalization.

Return to Summary Table

CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

Return to Summary Table

CRITERION 6: Relative acceptability of the test to patients (link to definition)

Cholescintigraphy
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

CT
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion). Patients may be required to hold their breath for a substantial period of time, which is seen as “uncomfortable” and “difficult,” particularly for patients with severe abdominal pain.[25]

ERCP
ERCP is a relatively invasive test. It involves inserting an endoscope through the patient’s mouth, and down the esophagus until it reaches the duodenum. Patients with altered surgical anatomy may not be suitable for ERCP, especially in cases where a Roux-en-Y anastomosis is required due to unusual anatomical features post-surgery.[16]

MRCP
MRCP is an MRI-based imaging test. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[26,27] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

Menon et al.[28] compared patient satisfaction in 34 patients who underwent both ERCP and MRCP. Patients completed a questionnaire using a Likert scale that measured anxiety, pain, and discomfort related to each test. Additionally, the patients rated their willingness to repeat each test and how difficult each test was, compared with their expectations. ERCP was rated as having statistically significant worse pain (ERCP 2.78, MRCP 2.44), and more discomfort (ERCP 3.09, MRCP 2.47) compared with MRCP. Although not statistically significant, patients were less willing to repeat ERCP than MRCP (ERCP = –1.30, MRCP = –0.72). ERCP was

found to be an easier test relative to expectations than MRCP. When patients were asked to directly compare ERCP with MRCP, ERCP was rated as more anxiety provoking, more painful, and more uncomfortable. These were all statistically significant except for the comfort domain. Patients also reported a higher preference for MRCP than ERCP.

U/S
Some discomforts associated with U/S include cold, unspecified pain, and tenderness. In a study comparing U/S with MRI in undiagnosed shoulder pain, 100% of the patients participating said that they would be willing to undergo the U/S exam again.[29] This test may be preferred in pediatric patients as there is no exposure to ionizing radiation, and the test does not require sedation.

Return to Summary Table

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

A study by Banzo et al.[10] evaluated the utility of hepatobiliary scintigraphy (cholescintigraphy) using ^{99m}Tc-mebrofenin for the diagnosis of bile leak in patients post liver transplant, who complained of abdominal pain after removal of the T-tube. A total of 20 patients with a mean age of 44 years old were enrolled, of which 13 were diagnosed with bile leak using cholescintigraphy, U/S, or ERCP. All 13 cases underwent cholescintigraphy; 10 cases were administered both cholescintigraphy and U/S; and six cases evaluated cholescintigraphy and ERCP. The results are presented for U/S compared with cholescintigraphy and ERCP compared with cholescintigraphy in Table 3.

Table 3: Bile Leaks Found by Cholescintigraphy Compared with Collections Identified by U/S and ERCP[10]

U/S	Cholescintigraphy		
	Positive	**Negative**	**Total**
Positive	8	1	9
Negative	1	0	1
Total	9	1	10
ERCP	**Cholescintigraphy**		
	Positive	**Negative**	**Total**
Positive	6	0	6
Negative	0	0	0
Total	6	0	6

ERCP = endoscopic retrograde cholangiopancreatography; U/S = ultrasound.

Based on the values in Table 3, the sensitivity and specificity of U/S was 88.89% and 0%, respectively. The sensitivity for ERCP was 100% compared with cholescintigraphy. With regard to the diagnostic accuracy of cholescintigraphy, it is sensitive for detecting bile leaks, but a negative result should be an indication for an ERCP. In addition, cholescintigraphy highlights the relationship between ultrasonographic collections and the biliary system.[10]

Trerotola et al.[5] evaluated the spectrum of biliary complications associated with laparoscopic cholecystectomy, and assessed various imaging modalities. Cases from December 1989 through July 1991 were reviewed and cholescintigraphy using ^{99m}Tc-disofenin, as well as U/S, CT, ERCP and percutaneous transhepatic cholangiography (an x-ray–based imaging modality), were included as comparators. During the review period, 13 patients were identified who met

the inclusion criteria. Bile leaks were considered minor complications and detection rates were reported. The detection rates for bile leak and stricture with ERCP were reported as a combined value of 88% (7/8). All other comparators reported detection rates for bile leak independently. Cholescintigraphy detected biliary complications in 100% of cases (6/6). CT (0/4) and US (0/3) were not able to detect bile leak, as the fluid collections shown during imaging were non-specific.[5]

Walker et al.[20] evaluated the disruption of the bile duct and biloma after laparoscopic cholecystectomy in 1991. A total of 263 case reports of laparoscopic cholecystectomies were reviewed and seven cases of bile leak and biloma were assessed to compare the imaging evaluation of CT, U/S, ERCP, and cholescintigraphy using the radiotracer ^{99m}Tc-diisopropyliminodiacetic acid (^{99m}Tc-DISIDA). Of the seven cases, five underwent cholescintigraphy and the sensitivities for each test were calculated using cholescintigraphy as the reference standard from the information provided.[20] U/S and CT scans identified fluid accumulations in the peritoneal cavity, while cholescintigraphy identified accumulations of radiolabelled bile.

Table 4: Bile Leaks Found by Cholescintigraphy Compared with Collections Identified by U/S[20]

U/S	**Cholescintigraphy**		
	Positive	**Negative**	**Total**
Positive	2 (1)	0	2
Negative	1 (2)	0	1
Total	3	0	3
CT	**Cholescintigraphy**		
	Positive	**Negative**	**Total**
Positive	4 (2)	0	4
Negative	0 (2)	0	0
Total	4	0	4
ERCP	**Cholescintigraphy**		
	Positive	**Negative**	**Total**
Positive	2 (2)	0	2
Negative	1 (1)	0	1
Total	3	0	3

CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; U/S = ultrasound.

In comparison to the cholescintigraphy using the radiotracer ^{99m}Tc-DISIDA, the sensitivities of U/S, CT, and ERCP were 67%, 100%, and 67%, respectively, when peritoneal fluid was used as an indicator of bile leak. If peritoneal fluid was not considered an indicator of bile leak, the respective sensitivities were 33%, 50%, and 67%. Specificity could not be calculated, as the prevalence of bile leak in the population observed was 100%.[20]

The authors concluded that CT and U/S were helpful in detecting abdominal fluid collections but could not differentiate bile from other fluids, while cholescintigraphy was quite useful. Cholescintigraphy would be a preferred method to ERCP as it is a non-invasive comparator; however, ERCP and percutaneous transhepatic cholangiography (PTC) may still be used to localize the exact point of leakage.[20]

Rayter et al.[49] enrolled 35 patients undergoing elective cholecystectomy for gallstones and determined the frequency of bile leaks. After the surgery, each patient underwent

cholescintigraphy and then immediately afterwards had a U/S scan. The results are presented in Table 5.

Table 5: Bile Leaks Found by HIDA Scanning Compared with Collections Identified by U/S[49]

U/S scan	HIDA scan		
	Positive	**Negative**	**Total**
Positive	5	15	20
Negative	6	9	15
Total	11	24	35

HIDA = hepatobiliary iminodiacetic acid scan; U/S = ultrasound.

Based on the values in Table 5, the specificity and sensitivity of the U/S scans are 37.5% and 45.5%, respectively.

MRCP

No information was found comparing the diagnostic accuracy of MRCP with cholescintigraphy in the detection of bile leak.

Pediatric population

In 2010, Lee et al.[8] conducted a retrospective review to evaluate the diagnostic usefulness of MRCP in the pediatric population where spontaneous bile duct perforation occurred. Cases from more than 10 years (March 1999 to February 2009) from a hospital database in Korea were reviewed, and three children were identified with the indication and relative comparator. MRCP was compared with U/S and cholescintigraphy using ^{99m}Tc-mebrofenin. In two of the three cases, MRCP, cholescintigraphy, and U/S were used in the detection of bile leak.

Table 6: Bile Leaks Found by Cholescintigraphy Scanning Compared with Collections Identified by U/S[8]

U/S	Cholescintigraphy		
	Positive	**Negative**	**Total**
Positive	1	0	1
Negative	1	0	1
Total	2	0	2
MCRP	**Cholescintigraphy**		
	Positive	**Negative**	**Total**
Positive	2	0	2
Negative	0	0	0
Total	2	0	2

MRCP = magnetic resonance cholangiopancreatography; U/S = ultrasound.

Based on the values in Table 6, the sensitivity of the U/S scan was 50% and the sensitivity for MRCP was 100% compared with cholescintigraphy. The authors concluded that U/S is the method of choice in children, but the field of view is limited. Cholescintigraphy provides useful information but exposes children to radiation and lacks anatomical information. MRCP was useful and able to detect fluid accumulation in all cases adjacent to the perforation site.

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CRITERION 8: Relative risks associated with the test (link to definition)
Non–radiation-related Risks

Cholescintigraphy
Risks associated with cholescintigraphy include allergy to HIDA, pain during cholecystokinin (CCK) injection (causes gallbladder contraction), chills, nausea, and rash.[30] Rapid administration of CCK has been associated with deterioration in blood gases and respiratory function in infants.[50] In a study of 18 subjects, slow infusion of CCK resulted in no adverse reactions, specifically abdominal pain, which was present in the group that had a bolus injection.[50] Slow infusion of CCK is now a well-recognized practice (MIIMAC expert opinion). In susceptible subjects, CCK has induced panic attacks.[50]

CT
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[31] In addition, patients may experience mild side effects from the contrast agent, such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and Gd contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found that 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[51] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. Specifically, Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media,*[52] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[52]

ERCP
ERCP is an invasive endoscopy-based procedure and can lead to further complications.[32] Prolonged cannulation may cause additional morbidity to patients and unnecessary radiation exposure.[33] ERCP is also associated with a high morbidity rate. In an uncontrolled prospective study conducted by Christensen, the procedure-related mortality rate was 1.0% in a population of 1,177 procedures, and overall 30-day mortality was 5.8%. Morbidity-related complications occurring in 15.8% of the population included pancreatitis, hemorrhage, perforation, cholangitis, perforated stent, and complications related to cardiac, respiratory, and thromboembolic systems.[34]

MRI
MRI is contraindicated in patients with metallic implants, including pacemakers.[35] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[31] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media,*[52] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[52]

U/S
There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

Among the modalities to diagnose bile leak, cholescintigraphy, CT, and ERCP expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 7.

Table 7: Effective Radiation Doses for Various Imaging Tests

Test	Effective Radiation Dose (mSv)	Pediatric Effective Dose Estimate Range (mSv)
^{99m}Tc-disofenin	3.1[36]	NR
^{99m}Tc-mebrofenin	3.1[36]	NR
CT	8.0[37]	8.0[37]
ERCP*	1 to 10[38]	0.3 to 3[38]
MRCP (MRI)	0	0
U/S	0	0
Average background dose of radiation per year	1-3.0[37,39,40]	1-3.0[37,39,40]

CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; GI = gastrointestinal; MRCP = magnetic resonance cholangiopancreatography; NR = not reported; ^{99m}Tc-disofenin = technetium-99m disofenin; ^{99m}Tc-mebrofenin = technetium-99m mebrofenin; U/S = ultrasound.
*Based on x-ray of abdomen and upper GI series with bowel follow-through.[38]

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

Cholescintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of hepatobiliary scans should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[53] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct cholescintigraphy. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and U/S should be diagnostic radiologists[41] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[53]

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on-site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[53]

CT
For the performance of CT scan, medical radiation technologists who are certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

ERCP
ERCP is an x-ray–based test performed by gastroenterologists. Gastroenterologists must have certification from the Royal College of Physicians and Surgeons of Canada (or Collège des médecins du Québec). ERCP is performed mostly by gastroenterologists with advanced endoscopy training, lasting one or two years after completion of the mandatory two-year subspecialty program.[54]

Expert endoscopists have a higher rate of successful cannulation, while novices have lower success rates and increased complication rates.[16]

Jowell et al.[55] completed a study evaluating the competency of gastroenterology fellows (at various stages of training) to complete an ERCP. Fellows performed this procedure under the watchful eye of an experienced therapeutic endoscopist. The fellows were graded on various technical aspects of the procedure, using a five-point scale: 1-excellent; 2-adequate; 3-partially successful; 4-failed; 5-no attempt. If the fellow achieved a score of 1 or 2, this was considered acceptable. Adequate skill in a particular component of the exam was arbitrarily defined as reflecting competency if the probability of an acceptable score was 0.8. The results of this study state that 160 ERCPs have to be done before a fellow achieves adequate skills. A more recent report states that the Canadian Association of Gastroenterology recommends at least 180 procedures should be performed before competence can be assessed.[56] According to the Endoscopy Committee of the Canadian Association of Gastroenterology, ERCP is one of the most technically demanding and highest-risk procedures performed by endoscopists.[54]

MRCP
Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

U/S
Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification from the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[41] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[41]

The availability of expertise to image bile leak varies across the jurisdictions. Table 8 reports the number of medical imaging professionals nationally and highlights those provinces and territories that lack a specific expertise. Gastroenterologists are not included in this list; however, the number of gastroenterologists in Canada available to perform the procedure is reported to be 1.83 per 100,000 persons.[57]

Table 8: Medical Imaging Professionals in Canada[41]						
Jurisdiction	**Diagnostic Radiology Physician**	**Nuclear Medicine Physician**	**Medical Radiation Technologists**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicist**
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PE	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdictions; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; ON = Ontario; PE = Prince Edward Island; QC = Quebec; YT = Yukon.
*This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 9 provides an overview of the availability of equipment required to diagnose bile leak. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Data were not available for U/S.

Table 9: Diagnostic Imaging Equipment in Canada[41,42]				
	Nuclear Medicine Cameras	**CT Scanners**	**MRI Scanners**	**SPECT/CT Scanners**
Number of devices	603[41]	460[42]	218[42]	96[42]
Average number of hours of operation per week (2006-2007)[41]	40	60	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	PE, YT, NT, NU

NT = Northwest Territories; NU = Nunavut; PE = Prince Edward Island; YT = Yukon

Cholescintigraphy
To perform cholescintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[41]

CT
No CT scanners are available in Nunavut.[42] The average weekly use of CT scanners ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[41] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[43]

ERCP
ERCP is an x-ray–based test. X-ray machines are widely available across the country.

MRCP
MRCP is an MRI based test. No MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[42] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario with a national average of 71 hours.[41] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[43]

U/S
U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[43]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of cholescintigraphy and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 9), the cost of cholescintigraphy with ^{99m}Tc-based radioisotopes is $247.85. CT is minimally more costly, MRCP is moderately more costly, and U/S is minimally less costly than cholescintigraphy. An estimate for ERCP could not be obtained; however, actual costs (i.e., excluding professional fees) obtained from one Ontario hospital were reported to be approximately $1900. Therefore, ERCP is a significantly more costly alternative.

Table 9: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[58]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
Cholescintigraphy				
J804	First transit — without blood pool images	16.50	20.95	37.45
J831	Biliary scintigraphy	117.45	50.95	168.4
Maintenance fees — from global budget		42.00		42.00
	TOTAL	175.95	71.90	**247.85**
CT				
X410	Abdominal CT — with IV contrast		102.65	102.65
X232	Pelvic CT — with IV contrast		102.65	102.65
Technical cost — from global budget		150.00		150.00
Maintenance fees — from global budget		28.55		28.55
	TOTAL	178.55	205.30	**383.85**
MRCP				
X451C	MRI — abdomen — multislice sequence		77.20	77.20
X455C (×3)	Repeat (another plane, different pulse sequence — to a maximum of 3 repeats)		115.95	115.95
X499C	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.50	65.40
X487C	Gadolinium		38.60	38.60
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		54.75		54.75
	TOTAL	354.75	297.25	**652.00**
U/S				
J135	Complete abdominal scan	50.00	34.95	84.95
Maintenance fees — from global budget		3.30		3.30
	TOTAL	53.30	34.95	**88.25**

3-D = three-dimensional; anes = anesthetic; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; prof = professional; spec = specialist; tech. = technical; U/S = ultrasound.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the technetium-99m (^{99m}Tc)-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
	burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1948 to March 14, 2011>
Date of Search:	March 15, 2011
Alerts:	Monthly search updates began March 14, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	No date limit English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Ovid MEDLINE Strategy	
Line #	**Search Strategy**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	radioisotope*.mp.
6	(technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc* or 99mtechnetium* or 99m-technetium*).tw,nm.

Ovid MEDLINE Strategy	
7	Radionuclide Imaging/ or Perfusion Imaging/
8	ri.fs.
9	((radionucl* or nuclear or radiotracer* or hepatobiliary or biliary or lidofenin or gadolinium-HIDA or Gd-HIDA or hepato-iminodiacetic acid or HIDA or 99mTc-IDA) adj2 (imag* or scan* or test* or diagnos*)).tw.
10	(SPECT or scintigraph* or scintigram* or scintiphotograph* or cholescintigraph*).tw.
11	Tomography, Emission-Computed, Single-Photon/
12	(single-photon adj2 emission*).tw.
13	(lidofenin or gadolinium-HIDA or Gd-HIDA or hepato-iminodiacetic acid or HIDA or 99mTc-IDA).tw,nm.
14	(59160-29-1 or 73121-98-9).rn.
15	or/1-14
16	Bile Duct Diseases/
17	exp Bile Ducts/in
18	Bile/
19	((bile or biliary) adj5 leak*).mp.
20	((bile duct* or biliary duct*) adj5 (complicat* or injur*)).tw.
21	or/16-20
22	Meta-Analysis.pt.
23	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
24	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
25	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
26	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
27	(data synthes* or data extraction* or data abstraction*).tw.
28	(handsearch* or hand search*).tw.
29	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.
30	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).tw.
31	(meta regression* or metaregression* or mega regression*).tw.
32	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
33	(medline or Cochrane or pubmed or medlars).tw,hw.
34	(cochrane or health technology assessment or evidence report).jw.

Ovid MEDLINE Strategy	
35	or/22-34
36	exp "Sensitivity and Specificity"/
37	False Positive Reactions/
38	False Negative Reactions/
39	du.fs.
40	sensitivit*.tw.
41	(predictive adj4 value*).tw.
42	distinguish*.tw.
43	differentiat*.tw.
44	enhancement.tw.
45	identif*.tw.
46	detect*.tw.
47	diagnos*.tw.
48	accura*.tw.
49	comparison*.tw.
50	Comparative Study.pt.
51	(Validation Studies or Evaluation Studies).pt.
52	Randomized Controlled Trial.pt.
53	Controlled Clinical Trial.pt.
54	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
55	Multicenter Study.pt.
56	(random* or sham or placebo*).ti.
57	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
58	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
59	(control* adj3 (study or studies or trial*)).ti.
60	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
61	(allocated adj "to").ti.
62	Cohort Studies/
63	Longitudinal Studies/
64	Prospective Studies/
65	Follow-Up Studies/
66	Retrospective Studies/
67	Case-Control Studies/
68	Cross-Sectional Study/
69	(observational adj3 (study or studies or design or analysis or analyses)).ti.
70	cohort.ti.

Ovid MEDLINE Strategy	
71	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
72	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
73	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
74	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
75	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
76	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
77	(population adj3 (study or studies or analysis or analyses)).ti.
78	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
79	or/36-78
80	Case Reports.pt.
81	79 not 80
82	15 and 21 and 35
83	limit 82 to english language
84	15 and 21 and 81
85	limit 84 to (english language and humans)

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 1, 2011	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 2011
Keywords:	Included terms for radionuclide imaging and biliary leak.
Limits:	No limits

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters), were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Definitions

Ascites: The accumulation of serous fluid in the peritoneal cavity.[59,60]

Anastomosis: The surgical or pathological connection of two tubular structures.[59,60]

Biloma: An encapsulated collection of bile in the peritoneal cavity.[61]

Peritoneal cavity: A potential space between the layers of the parietal and visceral peritoneum (membrane reflected over the viscera and the lining of the abdominal cavity). A small amount of fluid is contained in the space. Thus, friction is minimized as the viscera glide on each other, or against the wall of the abdominal cavity.[59,60]

Polydioxanone suture: Polydioxanone (PDS, Ethicon) is a monofilament absorbable suture that retains its integrity in tissues twice as long as any other synthetic absorbable suture. It is claimed to be slowly absorbed following hydrolysis, causing a minimal tissue reaction, and therefore should be less likely to promote infection.[59]

Roux-en-Y hepaticojejunostomy: Anastomosis of the distal divided end of the small bowel to another organ such as the stomach or oesophagus. The proximal end is anastomosed anastomosis of the hepatic duct to the jejunum.[59,60,62]

Sphincterotomy: Excision of any sphincter muscle.[59,60]

Appendix 4: Diagnostic Accuracy

Table 13: Diagnostic Accuracy of Hepatobiliary Scan and the Alternative Tests Based on the Information Presented in the Included Studies

Study	Population size/ (Mean Age)	Diagnostic accuracy of tests (%)				
		Chole	ERCP	U/S	CT	MRCP
Walker et al. 1992*	Seven patients post-cholecystectomy (mean age: 54 years)	Reference	*If collection of perihepatic fluid only used as detection* Sens: 67.7% *If collection of peritoneal fluid used as detection* Sens: 67.7%	*If collection of perihepatic fluid only used as detection* Sens: 33% *If collection of peritoneal fluid used as detection* Sens: 100%	*If collection of perihepatic fluid only used as detection* Sens: 50% *If collection of peritoneal fluid used as detection* Sens: 67.7%	NA
Banzo et al. 1998	13 patients post T-tube removal of liver transplantation (mean age: 44 years)	NA	Sens:100% Spec: NA	Sens: 88.89% Spec: 0%	NA	NA
Rayter et al. 1989*	35 patients undergoing elective cholecystectomy (mean age:56 years)	Reference	NA	Sens: 37.5% Spec: 45.5%	NA	NA
Lee et al. 2010	3 pediatric patient cases with spontaneous bile duct perforation (ages 3, 4, and 15 months)	Reference	NA	Sens:50% Spec: NA	NA	Sens:100% Spec: NA
Trerotola et al. 1992	13 patients post-cholecystectomy (mean age: 51 years)	*Detection rate* 100%	*Detection rate* 88%	*Detection rate* 0%	*Detection rate* 0%	NA

chole = cholescintigraphy; CT = computed tomography; ERCP = endoscopic retrograde cholangiography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; NA = not available; NLR = negative likelihood ratio; PLR = positive likelihood ratio; PPV: positive predictive value, sens = sensitivity; spec = specificity; U/S = ultrasound.

*Calculated using data provided in the article.

APPENDIX 2.3

INDICATION OVERVIEW

Pulmonary embolism (PE) is blockage of the main artery (or a distal branch of the main artery) that supplies blood to the lungs by material (typically a thrombus, or blood clot, but may also be a tumour, air, or fat) that originates elsewhere in the body, most commonly in the leg.[1] Severe obstruction of blood flow through the lungs causes increased pressure in the lungs, which also increases the right ventricle pressure load of the heart leading to PE symptoms. The clinical presentation of PE may range from asymptomatic disease to sudden death. The most common symptoms include unexplained breathlessness, chest pain, cough, hemoptysis, syncope, palpitations, rapid breathing, increased heart rate, cyanosis (bluish discoloration of the skin and mucous membranes caused by a lack of oxygen in the blood), fever, low blood pressure, right heart failure, pulmonary hypertension, and leg swelling.[2] However, these clinical symptoms are non-specific.[3] PE is categorized as either acute or chronic.[1] The focus of the current report is on the detection of acute PE. PE can be fatal, with a 30% mortality rate, but mortality can be significantly reduced with treatment.[1]

PE usually occurs secondary to inherited or acquired predisposing factors. Active cancers, recent immobilization or surgery, extremity paresis, hormone replacement therapy, factor V Leiden mutation, and oral contraceptives are among the acquired risk factors.[2,4] In 20% of patients, PE can be found without any identified predisposing factors.[5] Patients at risk for PE include those with deep vein thrombosis (DVT [a thrombus in a major venous system]) or patients taking medications that affect coagulation of the blood.

Imaging of PE allows for the mapping of blood flow in the lungs. The procedure allows for detection of the perfusion defect caused by the clot (embolus) but not the embolus itself.[6] Treatment is typically with anticoagulant therapy with fractionated heparin, low-molecular-weight heparin, or warfarin.[7]

Population: Patients with suspected acute pulmonary embolism (PE).

Intervention: Ventilation-perfusion scintigraphy (V/Q scan).

The basic principle of V/Q scanning is to recognize lung segments or sub-segments without perfusion but preserved ventilation; i.e., mismatch between the amount of air and blood reaching the gas exchange units in the lung.[2] A V/Q scan is a combination of two nuclear tests that involve administration of inhaled and intravenous radioisotopes to measure ventilation and perfusion in all areas of the lungs. The tests can be performed simultaneously or separately. A ventilation study is performed after inhalation of tracers such as xenon-133 (^{133m}Xe) gas, krypton (^{81m}Kr), or technetium-99m(^{99m}Tc)-labelled aerosols of diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) or ^{99m}Tc-labelled carbon microparticles (^{99m}Tc-technegas). Perfusion studies are performed after intravenous injection of ^{99m}Tc-labelled macroaggregated albumin (^{99m}Tc-MAA) particles. A gamma camera acquires images of the lungs and pulmonary vessels. Any mismatches — i.e., regions with normal ventilation image and a visible defect on the perfusion image — should be considered as a site of potential PE.[4]

V/Q scans can be performed using conventional planar scintigraphy or tomographic imaging (single- photon emission computed tomography [SPECT]) techniques.[2]

Comparators: For this report, computed tomography pulmonary angiography (CTPA) is considered as an alternative to V/Q scan:

CTPA: CTPA is an imaging test, used for the detection of PE, that employs computed tomography (CT). This test uses an intravenous radiographic contrast agent. Images are taken using a breath-hold technique. An acute PE can be seen as a filling defect in the pulmonary artery (complete or partial closure of the vessel).[8] Clinical signs and symptoms of PE, routine laboratory findings, chest X-rays, or cardiologic tests such as echocardiography are non-specific and their results are not always helpful in the diagnosis of PE.[4,9]

Clinical signs and symptoms of PE are helpful in the estimation of the clinical likelihood of PE before any diagnostic test is undertaken (pre-test probability), and to calculate later probability of the disease (post-test probability) using the information provided by appropriate diagnostic testing.[10-13] Measurement of the plasma concentration of D-dimer has been widely used as a non-invasive diagnostic test in patients with suspected PE. However, the utility of this test in the diagnosis of PE is limited due to its low specificity and positive predictive value.[9]

Lower limb compression ultrasonography is also indicated as a non-invasive diagnostic test in patients with suspected PE. This test is used for direct assessment of deep venous thrombosis (DVT) which can be associated with a higher risk of PE.[14,15] Thus, a positive test result can justify anticoagulant therapy and prevent the need for further investigation. However, because PE can occur in the absence of DVT, a negative test result does not necessarily exclude PE.[16] The accuracy of magnetic resonance imaging (MRI) techniques (e.g., real time MRI, MR angiography, MR perfusion imaging) for the diagnosis of PE has also been studied.[17,18] This modality is considered a safe and useful tool in patients with allergic reactions to iodine contrast materials (used for CTPA) or in patients for whom the radiation risk is a concern.[17] Various diagnostic algorithms have been developed to guide the use of combinations of multiple diagnostic tests to confirm or exclude PE.[19]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and pulmonary embolism.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. No date or human limits were applied to the HTA/SR/MA search. For primary studies, the retrieval was limited to documents published between January 1, 2006 and January 28, 2011, and the human population. Both searches were also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

There were 31 potential clinical articles identified through the MA/SR/HTA filtered search and 15 were subjected to full-text review. Of these, six reported on the relative diagnostic accuracy of V/Q scanning and CTPA in diagnosis of PE.[20-25] Two reviews[22,23] were excluded because they did not report summary estimates of diagnostic accuracy (i.e., sensitivity, specificity), and two[21,25] were excluded because they included older technologies. The two included analyses[20,24] were published in 2005. Different techniques (i.e., V/Q SPECT and V/Q planar and products (i.e., ^{133}Xe, ^{81m}Kr, ^{99m}Tc-DTPA, ^{99m}Tc-labelled technegas, ^{99m}Tc-MAA) may have been combined in some of the published analyses.

Four primary studies are included in the diagnostic accuracy section of this report; one comparing planar V/Q scintigraphy with V/Q SPECT[26] and three comparing V/Q scanning with CTPA.[27-29]

Finally, our search of the grey literature identified three guidelines on the prevention, diagnosis, and treatment of PE: those of the Institute for Clinical Systems Improvement (ICSI), the Scottish Intercollegiate Guidelines Network (SIGN), and the European Association of Nuclear Medicine (EANM).[2,30]

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	Each year, approximately 600,000 patients in the United States are diagnosed with a PE.[31,32] Of note, many more scans are performed to check for PE than the number of PE cases identified. Assuming the incidence rate in Canada is similar to that in the US, the size of the affected population is more than 1 in 1,000 (0.1%), and less than 1 in 100 (1%).
2	**Timeliness and urgency of test results in planning patient management**	Patients with suspected PE should be evaluated using appropriate diagnostic tests within the first 24 hours (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011) and receive anticoagulant therapy or installation of a central venous filter if the diagnosis is confirmed.[32] Not performing imaging can have a significant impact on patient management. The target time frame for performing the test is in 24 hours or less and obtaining the test results in a timely manner has significant impact on the management of the condition or the effective use of heath care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	The mortality rate of undiagnosed and untreated PE is 30%. However, a timely diagnosis and adequate treatment can reduce the mortality rate to 2% to 8%.[4,33] Diagnostic imaging test results can have significant impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Undiagnosed and untreated PE may lead to disabling morbidity from pulmonary hypertension (4% to 5%) and right ventricular failure,[4,34,35] and predispose patients to recurrent venous thromboembolism (2.5% for the first year following PE and 0.5% in successive years).[36,37] Diagnostic imaging test results can have moderate impact on morbidity or quality of life.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>5</td><td>Relative impact on health disparities</td><td>To be scored locally.</td></tr>
<tr><td>6</td><td>Relative acceptability of the test to patients</td><td>Patients having a V/Q scan are required to hold their breath for several seconds, which may be difficult. In addition, they are required to lie on their backs for up to 25 minutes. Patients undergoing CTPA are also required to hold their breath. The length of the CTPA procedure is shorter than a V/Q scan. One study evaluated patients' satisfaction for V/Q scan and CTPA. The proportion of the patients who rated their satisfaction as "good" or "very good" was 85.7% for spiral CT, compared to 14.3% for V/Q scanning.[38] The authors described the V/Q scans as being obtained using standard techniques; however, these techniques and the radiopharmaceutical used were not described in the study publication.

Although it is recognized that patient acceptability of V/Q scanning can vary depending on the techniques and the radiopharmaceutical used, it is assumed that V/Q scanning is minimally less acceptable to patients than CTPA.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>The most recent data on the relative diagnostic accuracy of V/Q scanning versus CT were found in four primary studies: one comparing planar V/Q scintigraphy with V/Q SPECT[26] and three comparing V/Q scanning to CTPA.[27-29]
<table>
<tr><th>Study</th><th>Modality</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td rowspan="2">Gutte et al., 2010[26]</td><td>V/Q SPECT</td><td>100 (79–100)</td><td>87 (78–87)</td></tr>
<tr><td>Planar V/Q</td><td>64 (40–83)</td><td>72 (61–80)</td></tr>
<tr><td rowspan="2">Gutte et al., 2009[27]</td><td>V/Q SPECT</td><td>97 (82–100)</td><td>88 (75–95)</td></tr>
<tr><td>CTPA</td><td>68 (49–83)</td><td>100 (93–100)</td></tr>
<tr><td rowspan="2">Miles et al., 2009[28]</td><td>V/Q SPECT</td><td>83 (61–95)</td><td>98 (92–100)</td></tr>
<tr><td>CTPA</td><td>NR</td><td>NR</td></tr>
<tr><td rowspan="2">Wang et al., 2009[29]</td><td>Planar V/Q</td><td>91.7</td><td>92.9</td></tr>
<tr><td>CTPA</td><td>100</td><td>92.9</td></tr>
</table>
CTPA = computed tomography pulmonary angiography; NR = not reported; SPECT = single-photon emission computed tomography; V/Q = ventilation-perfusion scintigraphy.

The discussion from MIIMAC members highlighted issues including location of the embolus and the lack of a gold standard. In large arteries, both V/Q and CTPA are able to detect PE;</td></tr>
</table>

<table>
<tr><th colspan="3">**Table 1:** Summary of Criterion Evidence</th></tr>
<tr><th colspan="3">**Domain 1:** Criteria Related to the Underlying Health Condition</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>however, in smaller arteries, V/Q scan is typically better.

Based on these results and expert opinion from MIIMAC members, V/Q SPECT and CTPA have similar diagnostic accuracies.</td></tr>
<tr><td>**8**</td><td>**Relative risks associated with the test**</td><td>**Non–radiation-related Risks**
V/Q scanning has been reported to be safe to use and few adverse reactions have been described.[4,39] The overall rate of adverse reactions to radiopharmaceuticals is reported to be between 1 to 2 per 100,000 doses.[39]

CTPA for PE requires an iodine-based contrast agent.The frequency of severe, life-threatening reactions with contrast are rare (0.001% to 0.01%).[40] Moderate reactions resembling an allergic response are also very unusual and range in frequency from 0.004% to 0.7%.[40]

Radiation-related Risks
Among the modalities to detect pulmonary embolism, both V/Q scanning and CTPA expose the patient to ionizing radiation. In general, CTPA confers larger doses of radiation than V/Q scanning.

Effective Doses of Radiation[41,42]
Procedure | **Average Dose Range (mSv)**
V/Q scan | 0.21 to 2.4
CTPA | 4.2 to 19.9
CTPA = computed tomography pulmonary angiography; mSv = millisievert; V/Q = ventilation-perfusion scintigraphy

In general, V/Q scanning is minimally safer than CT.</td></tr>
<tr><td>**9**</td><td>**Relative availability of personnel with expertise and experience required for the test**</td><td>As of 2006, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, 1,781 nuclear medicine technologists, and 2,900 sonographers available across Canada. Yukon, Northwest Territories, and Nunavut do not have the available personnel to perform and interpret tests to detect PE. Other jurisdictions (e.g., Prince Edward Island) may offer limited nuclear medicine services.</td></tr>
</table>

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<tr><th colspan="3">**Table 1:** Summary of Criterion Evidence</th></tr>
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<tr><td></td><td></td><td>Depending upon the centre, and assuming the necessary equipment is available, it is estimated that more than 95% of procedures could likely be performed in a timely manner using CTPA.</td></tr>
<tr><td>**10**</td><td>**Accessibility of alternative tests (equipment and wait times)**</td><td>For V/Q scans, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[43]

A report from the CIHI states that, as of January 1, 2007, CT scanners were available at a rate of 12.8 per million people in Canada; however, there were none available in Nunavut.[43] For CT scanners, the average weekly use ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[43] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[44]

Depending upon the centre and assuming the necessary expertise is available, it is estimated that more than 95% of procedures could be performed in a timely manner using CTPA.</td></tr>
<tr><td>**11**</td><td>**Relative cost of the test**</td><td>According to our estimates, the cost of V/Q scanning is $295.23 ($370.93 for SPECT). CTPA is a minimally less costly alternative.

Relative Costs
Test | **Total Costs ($)** | **Cost of Test Relative to ^{99m}Tc-based Test ($)**
V/Q Scan | 370.93 | Reference
CTPA | 266.41 | –104.52</td></tr>
</table>

CIHI = Canadian Institute for Health Information; CT = computed tomography; CTPA = computed tomography pulmonary angiography; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; PE = pulmonary embolism; SPECT = single-photon emission computed tomography; V/Q = ventilation-perfusion scintigraphy.

CRITERION 1: Size of affected population (link to definition)

PE is the third most common acute cardiovascular emergency after myocardial infarction and stroke,[45] and is estimated to be responsible for 5% to 10% of all deaths in United States hospitals.[46]

The accurate size of population affected by PE is difficult to obtain because most pulmonary emboli are detected on autopsy. About 80% of patients with an identified PE at autopsy are unsuspected or undiagnosed before death.[15] The prevalence of PE in patients who are clinically suspected is only 30%.[21] Approximately 600,000 patients each year are diagnosed with PE in the United States.[31,32] The corresponding figures for Canada are unavailable. PE was reported to be the cause of death in more than 545 Canadians in 2007.[47]

PE and DVT are different manifestations of a single condition named venous thromboembolism (VTE).[48] The annual incidence of VTE is approximately one in 1,000 persons.[32] Among patients with DVT, 32% have a clinically silent (asymptomatic) PE diagnosed by lung scan, pulmonary angiography, or CT scan.[14,15] Therefore, routine screening for PE in patients with DVT has been suggested.[15] In 79% of patients with PE, DVT can be found in lower limbs if sensitive diagnostic methods are used.[49]

The results of the National Hospital Discharge Survey showed that the incidence of PE in hospitalized patients was 0.40% (95% CI, 0.39% to 0.40%) and did not change over the period of 1979 to 1999.[50] The incidence rates were similar in women and men, and amongst Whites and Blacks.[50] DeMonaco et al. reviewed PE hospital discharge data from the Pennsylvania Health Care Cost Containment Council to estimate PE incidence rates from 1997 to 2001. Based on the results of this study, the incidence of PE increased from 47 per 100,000 patients to 63 per 100,000 patients during the five-year period (mean increase of 0.004% per year).[51] This mean annual increase in risk was significantly higher in women than men (0.013%), in African-American race than Whites (0.031%), and in patients who were more than 70 years old (0.0007%; $P < 0.0001$ for all). However, there was a significant decrease in the severity of illness scores. The authors discussed that the increasing incidence of PE could be due to increasing early diagnosis of PE after introduction of spiral CT in the state of Pennsylvania.[51]

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Undiagnosed or untreated PE can be fatal or result in disabling morbidity from pulmonary hypertension or recurrent PE in survivors.[34] A timely and adequate treatment with anticoagulants/central venous filter can reduce mortality and morbidity.[4] Conversely, incorrect diagnosis of the condition unnecessarily exposes patients to the risk of anticoagulant therapy, which can result in adverse effects and bleeding complications (about 3%).[52] Therefore, patients suspected of having PE should be promptly evaluated using appropriate diagnostic tests and receive anticoagulant therapy if the diagnosis is confirmed.[32]

According to the Saskatchewan hospital guidelines, V/Q lung scan or CT scan should be performed within the first 24 hours in patients with suspected acute PE (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011).

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Untreated PE can be rapidly fatal, and some survivors of undiagnosed PE can suffer disabling morbidity from pulmonary hypertension.[31,34]

The mortality rate of undiagnosed and untreated PE is 30%. However, a timely diagnosis and adequate anticoagulation therapy can reduce the mortality rate to 2% to 8%.[4,33]

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Undiagnosed and untreated PE may lead to disabling morbidity from pulmonary hypertension and right ventricular failure,[4,34] and predispose patients to recurrent VTE.[36] Pulmonary hypertension occurs in 4% to 5% of patients following PE,[35] with a probability of 31% in the first year following PE and 38% in successive years.[35]

Undiagnosed and untreated PE may also lead to potentially fatal early recurrences.[4] The likelihood of PE recurrence is 2.5% for the first year following PE and 0.5% for successive years.[37]

Return to Summary Table.

CRITERION 5: Relative impact on health disparities (link to definition)

Health disparity might be present if disadvantaged social groups systematically experience poorer health or more health risks than do more advantaged social groups.[53] Disadvantaged groups can be defined based on gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs. Our targeted search found disparity concerns in the following disadvantaged groups:

Residents of rural and remote areas
Much of the medical imaging equipment and expertise required for the diagnosis of PE are unavailable or inaccessible to residents of rural areas (refer to Criterion 10 — Accessibility of alternative tests — for more information).Therefore, timely diagnosis of PE is less likely in rural or remote facilities.[54] Given the emergent nature of PE, the unavailability of appropriate diagnostic tests may lead to missed diagnosis or unnecessary anticoagulation.[54]

Ethnic and racial groups
In the United States, the incidence of VTE has been shown to be 30% to 50% higher in African-Americans than in Whites.[55-58] American Indians, Alaskan Natives, and Asians have been reported to have a significantly lower rate of PE as compared to Blacks and Whites.[55,56] African-Americans have also been shown to have a 30% higher chance of mortality within 30 days following the diagnosis of PE.[59] Although factors such as genetics or other comorbid conditions (e.g., obesity and diabetes) can directly or indirectly impact the incidence of PE, the above-mentioned differences in incidence and mortality rates can be attributable to disparities in diagnosis and care.[60]

Women and children
V/Q scanning and spiral CT involve exposure to ionizing radiation. This can be a concern in testing pediatric patients, as the risk of radiation-induced cancer is shown to be two to three times greater in children and adolescents than in adults.[39] The risk of pulmonary embolism increases during pregnancy.[39] At the same time, there is concern regarding fetal exposure to radiation with either V/Q scanning or CTPA.[39] V/Q SPECT is generally recommended as first line in this special population.[39]

CTPA delivers relatively high doses of radiation to the breast and lung tissues. This can pose a greater risk of radiation-induced breast cancer to young women who have breast tissue with a higher cellular turnover rate. The estimated radiation dose from CTPA (10 to 70 millisievert [mSv]) is much greater than V/Q scan (less than 1.5 mSv).[39] Based on the most recent Biologic Effects of Ionizing Radiation report (BEIR VII),[61] the lifetime attributable risk of breast cancer from a breast dose of 20 milligrays (mGy) delivered by CTPA is approximately 1/1,200 for a woman aged 20, 1/2,000 for a woman aged 30, and 1/3,500 for a woman aged 40.[39] A V/Q scan is therefore preferred over CTPA in young women with suspected PE.[62]

Return to Summary Table.

CRITERION 6: Relative acceptability of the test to patients (link to definition)

V/Q scanning
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

CT
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion). Patients may be required to hold their breath for a substantial period of time, which is seen as “uncomfortable” and “difficult.”[63]

V/Q scanning versus CT
In a prospective study published in 2005, Katsouda et al.[38] evaluated patient satisfaction with spiral CT versus V/Q scanning in 63 patients who were clinically suspected of having PE. All patients underwent sequential testing with V/Q scanning and contrast-enhanced spiral CT. The primary outcome of the study was diagnostic accuracy, and patient satisfaction was measured as a secondary outcome. The proportion of the patients who rated their satisfaction as “good” or “very good” was 85.7% for spiral CT, as compared with 14.3% for V/Q scanning. The authors described the V/Q scans as being obtained using standard techniques; however, these techniques and the radiopharmaceutical used were not described in the study publication.

Return to Summary Table.

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Guidelines

Our search of the grey literature identified three guidelines on the prevention, diagnosis, and treatment of PE.[2,30] Their recommendations, as they pertain to imaging and the detection of PE, are described, as follows:

An eleventh edition of the Institute for Clinical Systems Improvement (ICSI) guidelines for venous thromboembolism diagnosis and treatment was published in March 2011.[64] These guidelines recommend CTPA as the first line study of choice, unless a contraindication exists.[64] In cases where a contraindication exists, V/Q scan is recommended instead.[64]

The 2010 Scottish Intercollegiate Guidelines Network (SIGN) guidelines for the prevention and management of venous thromboembolism also recognize CTPA as the gold standard for detecting acute pulmonary embolus.[65] Again, in cases where CTPA is contraindicated, the authors recommend isotope lung scintigraphy (V/Q scan).[65]

The European Association of Nuclear Medicine (EANM) guidelines for V/Q scan,[2,30] published in 2009, express a preference for V/Q SPECT over planar V/Q. They further recommend technegas as the radioaerosol of choice for ventilation scintigraphy in patients with chronic obstructive pulmonary disease.[2,30]

Systematic reviews and meta-analyses

Six systematic reviews and meta-analyses identified in the literature search reported on the relative diagnostic accuracy of V/Q scanning and CTPA in the diagnosis of PE.[20-25] Two reviews[22,23] were excluded because they did not report summary estimates of diagnostic accuracy (i.e., sensitivity, specificity), and two[21,25] were excluded because they included older technologies and therefore their estimates of diagnostic performance were deemed out-of-date. The two included analyses[20,24] were published in 2005. Different techniques (i.e., V/Q SPECT and V/Q planar) and products (i.e., ^{133m}Xe, ^{81m}Kr, ^{99m}Tc-DTPA, ^{99m}Tc-labelled technegas, ^{99m}Tc-MAA) may have been lumped together in some of the analyses.

Hayashino et al.(2005)[20] conducted a meta-analysis comparing helical (spiral CT) or V/Q scanning in the diagnosis of PE with pulmonary angiography as the gold standard. The authors searched the English language articles in MEDLINE from 1990 to 2003 for helical CT and from 1985 to 2003 for V/Q scan. Helical CT articles were searched from 1990 onwards, as the earlier CT equipment was different. Twelve articles were included in the review: Two of the studies compared helical CT and V/Q scanning to angiography, seven compared CT alone to angiography, and three compared V/Q alone to angiography. The ventilation studies included in the review used ^{133}Xe, ^{99m}Tc-pyrophosphate (PYP), or ^{99m}Tc-DTPA, as the radioisotope and perfusion studies used ^{99m}Tc-MAA.[20] To calculate the sensitivity and specificity of the tests, three thresholds were specified based on the prospective investigation of the pulmonary embolism diagnosis (Prospective Investigation of Pulmonary Embolism Diagnosis or PIOPED) criteria (high, intermediate, low, near normal, or normal pre-test probabilities of PE).[66] A random effects model was used to pool the data from the studies (Appendix 3). A summary receiver operating characteristic (ROC) analysis that summarizes the sensitivity and specificity of different tests into a single ROC curve was used for the indirect comparison of CTPA versus V/Q scan. Based on the results of the meta-analysis and ROC analysis, the authors concluded that helical CT and V/Q scanning had similar discriminatory power when the high probability threshold was used. They also suggested that helical CT could be superior to V/Q scanning, in terms of discriminatory power, when normal or near normal threshold was used.

Roy et al.(2005)[24] conducted a systematic review of literature published between 1990 and 2003 in order to assess the likelihood ratios of the diagnostic tests used to detect PE. Overall, 48 studies were included in this review, including two studies of V/Q scan and seven studies of CTPA. The authors were unable to pool the results of the studies evaluating V/Q scanning. The pooled random positive likelihood ratio for CT was 24.1.

Primary studies

Gutte et al. (2010)[26] conducted a prospective study comparing V/Q SPECT and planar V/Q lung scanning in diagnosing acute PE. Both of these technologies were performed using ^{99m}Tc-MAA, but the results are included here to assist in the interpretation of other comparisons.[26] Among the 36 study participants, V/Q SPECT was found to have a sensitivity of 100% and a specificity of 87%.[26] In comparison, planar V/Q scanning was both less sensitive (64%) and less specific (72%).[26]

In a 2009 publication, the same group of researchers assessed the diagnostic ability of V/Q SPECT compared with multidetector computed tomography in patients with suspected PE.[27] Eighty-one patients were included in the analysis.[27] Final diagnoses were made using all available information: electrocardiography, sonography, D-dimer levels, clinical data, and follow-up from hospital files and telephone interviews.[27] Diagnostic performance was measured for sensitivity, specificity, positive predictive value, negative predictive value, and accuracy (Table 2).[27] The authors concluded that lung scintigraphy performed as V/Q SPECT, in combination with low-dose CT without contrast enhancement, should be considered as first-line in the work-up of PE, where possible.[27]

Table 2: Diagnostic Performance of SPECT versus CT[27]

Modality	Sens. (%)*	Spec. (%)*	PPV (%)*	NPV (%)*	Acc. (%)*	Non-diagnostic Rate (%)*
V/Q SPECT	97 (82-100)	88 (75-95)	82 (65-93)	98 (88-100)	91 (83-93)	5 (1-12)
V/Q SPECT plus low-dose CT	97 (83-99)	100 (93-100)	100 (88-100)	98 (90-100)	99 (93-100)	0 (0-4)
Perfusion SPECT plus low-dose CT	93 (81-98)	51 (43-55)	57 (49-60)	91 (76-98)	68 (58-72)	17 (10-28)
Pulmonary MDCT angiography	68 (49-83)	100 (93-100)	100 (84-100)	83 (71-92)	88 (78-94)	0 (0-4)

Acc. = accuracy; MDCT = multidetector computed tomography; NPV = negative predictive value; PPV = positive predictive value; Sens. = sensitivity; Spec. = specificity; V/Q SPECT = ventilation/perfusion single-photon emission computed tomography.
*Values in parenthesis are 95% confidence intervals.

An Australian study by Miles et al. (2009) also compared SPECT V/Q scintigraphy and CTPA in the diagnosis of PE.[28] The sensitivity and specificity of SPECT were calculated against a reference diagnosis based on all available information, made by a panel of respiratory physicians.[28] Sensitivity and specificity values for CTPA were not calculated, but concordance between SPECT and CTPA was presented.[28] One hundred patients with clinically suspected acute PE were recruited; 99 underwent planar V/Q scanning, 87 underwent SPECT V/Q scanning, and 95 underwent CTPA.[28] SPECT was found to have a sensitivity of 83%, a specificity of 98%, and to agree with CTPA diagnosis in 95% of cases.[28]

A third study investigated the relative diagnostic performance of V/Q scanning, compared with CT, in the diagnosis of PE.[29] Eighty-two patients were included in the analysis; 42 underwent CTPA with a 16-detector CT and 40 with a 64-detector CT. Twenty-eight patients underwent V/Q scanning using ^{99m}Tc-MAA for perfusion scanning and ^{99m}Tc-DMSA for ventilation scanning.[29] A single-head gamma camera was used for imaging.[29] Two patients with non-diagnostic scans were excluded from the analysis.[29] The authors found the sensitivities of both CTPA and V/Q scanning to be 91.7%. CTPA outperformed V/Q scanning in specificity (100.0% versus 92.9%).[29]

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related risks

V/Q Scan
V/Q test has been reported to be safe to use and few allergic reactions have been described.[4,39] The overall rate of adverse reactions to radiopharmaceuticals is reported to be one to two per 100,000 doses.[39] Allergies and adverse reactions to ^{99m}Tc-MAA were reported in the 1970s,[39,67] but there have been no adverse events to modern V/Q scanning techniques reported, as the size and number of radionuclide particles are much smaller now than they were in the 1970s.[67] V/Q scan is associated with no toxicity to body organs.[67]

CT
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[68] In addition, patients may experience mild side effects from the contrast agent such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found that 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[69] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. Contrast is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[40] the frequency of severe, life-threatening reactions with gadolinium are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[40]

Radiation-related risks
Among the modalities to detect pulmonary embolism, both V/Q scanning and CTPA expose the patient to ionizing radiation. Table 3 summarizes the estimated effective dose of radiation in adults, as well as the estimated dose absorbed by mother and fetus during pregnancy for the aforementioned tests. As the table shows, in general CTPA carries larger doses of radiation than V/Q scanning does. However, during the first and second trimesters of pregnancy, V/Q scans are associated with a higher fetal absorbed radiation dose compared with CTPA.

Table 3: Estimated of Effective Radiation Dose (mSv) from V/Q Scanning and CTPA[39]								
Patient Group		**V/Q Scan**			**CTPA**			
		Ventilation ^{99m}Tc-DTPA*	**Ventilation Technegas†**	**Perfusion ^{99m}Tc-MAA‡**	**Single slice**	**4-slice**	**16-slice**	**64-slice**
Adult		0.21	0.75	2.4	NA	4.2	14.4	19.9
Pregnant women	Breast	0.04	0.13	0.6	NA	NA	10 to 20	NA
	Lung	0.3	2.2	6.7	NA	NA	10	NA
Fetus	Early	0.12	0.008	0.35	NA	NA	0.24 to 0.47	NA
	1st trimester	0.09	0.008	0.48	0.003 to 0.020	NA	0.61 to 0.66	NA
	2nd trimester	0.05	0.010	0.55	0.008 to 0.077	NA	NA	NA
	3rd trimester	0.06	0.012	0.46	0.051 to 0.131	NA	0.06 to 0.23	NA

CTPA = computed tomography pulmonary angiography; DTPA = diethylenetriamine pentaacetic acid; MAA = macroaggregated albumin; mSv = millisievert; NA = not available; ^{99m}Tc = technetium-99m; V/Q = ventilation/perfusion scintigraphy.

*30 megabecquerels (MBq) in adults and 20 MBq in pregnancy.
†50 MBq in adults and 20 MBq in pregnancy.
‡200 MBq in adults and 100 MBq in pregnancy.

Return to Summary Table.

CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to detect a PE are presented by imaging modality. A summary of the availability of personnel required for the conduct of methods to detect a PE, by V/Q scan or CT, is provided in Table 4.

V/Q scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of V/Q scans should be nuclear medicine physicians or diagnostic radiologists with training and expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct V/Q scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans should be diagnostic radiologists[43] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the

Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial licence.[70]

Medical radiation technologists (MRTs) must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on-site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners and nuclear medicine equipment.[70]

CT
For the performance of CT scan, medical radiation technologists who are certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

Table 4: Medical Imaging Professionals in Canada, 2006[43]

Jurisdiction	Diagnostic Radiology Physician	Nuclear Medicine Physician	Medical Radiation Technologists	Nuclear Medicine Technologists	Medical Physicists
NL	46	3	263	15	NR
NS	71	5	403	71	NR
NB	47	3	387	55	NR
PEI	7	0	57	3	0
QC	522	90	3,342	460	NR
ON	754	69	4,336	693	NR
MB	58	8	501	42	NR
SK	61	4	359	36	NR
AB	227	18	1,229	193	NR
BC	241	21	1,352	212	NR
YT	0	0	0	0	0
NT	0	0	26	1	0
NU	0	0	0	0	0
Total	**2,034**	**221**	**12,255**	**1,781**	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; ON = Ontario; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 5 provides an overview of the availability of equipment required to detect pulmonary embolism.

Table 5: Diagnostic Imaging Equipment in Canada, 2007[43]

	Nuclear Medicine Cameras	CT Scanners	SPECT/CT Scanners
Number of devices	603	419	35
Devices per million people	18.4	12.8	1.6
Average number of hours of operation per week (2006-2007)	40	60	n/a
Provinces and territories with no devices available	*YT, NT, NU*	*NU*	*NL, PEI, NS, MB, AB, YT, NT, NU*

AB = Alberta; CT = computed tomography; MB = Manitoba; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; SPECT/CT = single-photon emission computed tomography/computed tomography; YT = Yukon.

V/Q Scanning

For V/Q scans, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[43]

CT

A report from the Canadian Institute for Health Information states that, as of January 1, 2007, CT scanners were available at a rate of 12.8 per million people in Canada; however, there were none available in Nunavut.[43] For CT scanners, the average weekly use ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[43]

In 2010, the average wait time for a CT scan in Canada was 4.2 weeks.[44]

Return to Summary Table.

CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of V/Q scanning and CTPA. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 6), the cost of V/Q scanning is $295.23 ($370.93 for SPECT). CTPA is a minimally less costly alternative.

Table 6: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[71]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
V/Q scan				
J860	Perfusion and ventilation scintigraphy — same day	176.25	62.80	244.45
J866	Application of tomography (SPECT)	44.60	31.10	75.70
Maintenance fees — from global budget		50.78		50.78
	TOTAL	271.63	93.90	**370.93**
CTPA				
X407	CT — Thorax — with IV contrast		79.85	79.85
Maintenance fees — from global budget		36.56		36.56
Technical cost — from global budget		150.00		150.00
	TOTAL	186.56	79.85	**266.41**

CT = computed tomography; CTPA = computed tomography pulmonary angiography; IV = intravenous; Prof. = professional; SPECT = single-photon emission computed tomography; Tech. = technical; V/Q = ventilation/perfusion.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Clinical Uses	
Criterion	**Definition**
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

Overview	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1948 to January 28, 2011>
Date of Search:	January 31, 2011
Alerts:	Monthly search updates began January 31, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	No date limit for systematic reviews; publication years 2006 – January 2011 for primary studies English language Human limit for primary studies

Syntax Guide	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Ovid MEDLINE Strategy	
Line #	**Search Strategy**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	radioisotope*.mp.
6	(technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.

Ovid MEDLINE Strategy	
7	Perfusion Imaging/ or Radionuclide Imaging/
8	Pulmonary Embolism/ri
9	Lung/ri
10	Pulmonary Ventilation/
11	(gamma camera imag* or perfusion imaging or radionuclide imaging or radionuclide scan* or lung perfusion or nuclear medicine test* or scintigraph* or scintigram* or scintiphotograph*).tw.
12	(ventilation-perfusion adj5 (imaging or scan* or scintigraph* or SPECT)).mp.
13	("ventilation/perfusion" adj5 (imaging or scan* or scintigraph* or SPECT)).mp.
14	((ventilation and perfusion) adj5 (imaging or scan* or scintigraph* or SPECT)).mp.
15	((VQ or V-Q or "v/q") adj5 (imaging or scan* or scintigraph* or SPECT)).mp.
16	or/1-15
17	Pulmonary Embolism/
18	(pulmonary adj2 (embolism* or embolus or emboli or thromboembolism* or thrombo-embolism*)).tw.
19	or/17-18
20	Meta-Analysis.pt.
21	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
23	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
25	(data synthes* or data extraction* or data abstraction*).tw.
26	(handsearch* or hand search*).tw.
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.
28	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).tw.
29	(meta regression* or metaregression* or mega regression*).tw.
30	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
31	(medline or Cochrane or pubmed or medlars).tw,hw.
32	(cochrane or health technology assessment or evidence report).jw.
33	or/20-32
34	exp "Sensitivity and Specificity"/

Ovid MEDLINE Strategy	
35	False Positive Reactions/
36	False Negative Reactions/
37	du.fs.
38	sensitivit*.tw.
39	(predictive adj4 value*).tw.
40	distinguish*.tw.
41	differentiat*.tw.
42	enhancement.tw.
43	identif*.tw.
44	detect*.tw.
45	diagnos*.tw.
46	accura*.tw.
47	comparison*.tw.
48	Comparative Study.pt.
49	(Validation Studies or Evaluation Studies).pt.
50	Randomized Controlled Trial.pt.
51	Controlled Clinical Trial.pt.
52	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
53	Multicenter Study.pt.
54	(random* or sham or placebo*).ti.
55	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
56	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
57	(control* adj3 (study or studies or trial*)).ti.
58	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
59	(allocated adj "to").ti.
60	Cohort Studies/
61	Longitudinal Studies/
62	Prospective Studies/
63	Follow-Up Studies/
64	Retrospective Studies/
65	Case-Control Studies/
66	Cross-Sectional Study/
67	(observational adj3 (study or studies or design or analysis or analyses)).ti.
68	cohort.ti.
69	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.

Ovid MEDLINE Strategy	
70	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
71	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
72	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
73	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
74	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
75	(population adj3 (study or studies or analysis or analyses)).ti.
76	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
77	or/34-76
78	Case Reports.pt.
79	77 not 78
80	16 and 19 and 33
81	limit 80 to english language
82	16 and 19 and 79
83	limit 82 to (english language and humans and yr="2006 -Current")

Other Databases	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 1, 2011	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

Grey Literature Searching	
Dates for Search:	February 2011
Keywords:	Included terms for radionuclide imaging and pulmonary embolism.
Limits:	No limits

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Definitions

Millisievert (mSv): The sievert — named after Rolf Sievert, a Swedish medical physicist — is a unit of dose equivalence. It shows the biological effects of radiation as opposed to the physical aspects, which are characterized by the absorbed dose (see milligray, below). A millisievert is one-thousandth of a sievert.

MilliGray (mGy): The gray — named after Louis Harold Gray, a British physicist — is a unit of absorbed radiation dose of ionizing radiation (e.g., X-rays). It is defined as the absorption of one joule of ionizing radiation by one kilogram of human tissue.

Visual Analog Scale (VAS): A visual analog scale usually consists of a single horizontal line on a page, with verbal and numerical descriptors at each end. Vertical lines and sometimes numbers are added to make scale units. One end point of the line (usually denoted as 10 or 100) is labelled as “the best health state possible,” and the opposite end point (denoted as 0) is labelled as “the worst health state possible.”

APPENDIX 2.4

INDICATION OVERVIEW

Bone fracture or break is the result of stress on the bone. Fracture can result from a variety of reasons, but the most common types include traumatic fracture, insufficiency fracture, and stress fracture. Traumatic fractures are the most common and result from accidental causes (e.g., severe fall, motor vehicle accident) or non-accidental or intentional causes (i.e., abuse). Insufficiency fractures occur when the quality of bone is insufficient to handle the normal stress of weight bearing (e.g., osteoporosis). Stress (or fatigue) fractures are associated with repetitive load-bearing stress to a normally healthy bone, common among athletes (e.g., gymnasts, dancers, long-distance runners) and military personnel.[1,2]

Imaging of suspected fracture usually begins with plain radiography (x-ray). Although x-ray will reveal most fractures, subtle fractures, including those in skeletally immature children, and some stress fractures may not be visible immediately on x-ray. If symptoms of fracture persist, an occult (or hidden) fracture is suspected. Follow-up x-rays may show a fracture due to loss of bone around the fracture site during the healing process. However, if plain x-rays continue to be negative but clinical suspicion remains, further imaging tests (i.e., bone scintigraphy, magnetic resonance imaging [MRI], or computed tomography [CT]) are warranted.

Population: Adults with suspected osteoporotic fracture or stress fracture.

Note: although not identified as a population of interest for this indication, relevant fracture data relating to children are presented in Appendix 5.

Intervention: Radionuclide bone scintigraphy (bone scan) using technetium-99m (^{99m}Tc)-labelled pharmaceuticals.

Bone scintigraphy is one of the most frequently performed nuclear medicine procedures for the detection of bone disorders.[4,5] Canadian 2006 data indicate that 17% of the supply of ^{99m}Tc was used in bone scintigraphy.[6] Although protocols may vary between institutions, the most common method of administering bone scintigraphy is the three-phase radionuclide examination. Prior to these phases, approximately 25 millicurie (mCi) of ^{99m}Tc-labelled radiopharmaceutical is injected into the patient who is positioned under a gamma camera. Images are then obtained through the following three phases:[7]

- *Phase 1*: Blood flow/dynamic phase: This phase occurs almost immediately after the administration of the ^{99m}Tc radiopharmaceutical and is obtained over the area being examined.
- *Phase 2*: Blood pool phase: occurs five to 10 minutes after the blood flow phase. Images are acquired by a gamma camera. Note: uptake of radiotracer within bone is influenced by blood flow and rate of new bone formation.[4,8]
- *Phase 3:* Delayed images: occurs 1.5 to five hours after injection of radiopharmaceutical (time varies according to age).

The gamma camera images reflect osteoblast (bone cells involved in new bone formation) cell activity in the bones. The delay between injection and imaging allows clearance of the radiotracer from the soft tissues, resulting in a higher target-to-background ratio and improved visualization of bone.[9] Areas that absorb little or no amount of tracer appear as "cold" spots, which can indicate a lack of blood supply to the bone (bone infarction) or the presence of certain types of cancer. Areas of rapid bone growth or repair absorb increased amounts of the tracer and show up as "hot" spots in the pictures. Hot spots can indicate the presence of a fracture, tumour, or an infection. Although most skeletal trauma is evaluated by radiography, some injuries are occult, and bone scintigraphy can detect changes as early as a few hours after injury.[10] Hence, bone scintigraphy often has a complementary role to radiography in fracture assessment, most notably in children younger than two years with suspected non-accidental fracture[11] or occult osteoporotic fractures.[5]

Comparators: For this report, the following diagnostic tests are considered as alternatives to bone scintigraphy:

- *Computed Tomography (CT):* CT (also known as computed-assisted tomography or CAT) creates three-dimensional images of body tissues and organs using x-ray images processed by a computer.[12]
- *Magnetic Resonance Imaging (MRI):* MRI uses three components to generate detailed images of internal organs and tissues — hydrogen atoms in the tissues, a powerful cylindrical external magnet to generate a magnetic field around the subject, and radiofrequency coils to generate intermittent radio waves.[12] In a strong magnetic field, atoms tend to line up like iron filings around a bar magnet. A pulse of radiofrequency radiation (like that used in a microwave oven) disturbs that alignment. When the atoms return to their former state, they emit the energy from the radiation that reveals their molecular environment and spatial location. MRI imaging techniques can be enhanced by injection of contrast agents such as gadolinium (Gd).[12]
- *Positron Emission Tomography (PET):* PET is a nuclear medicine exam used to create images of the inside of the body by measuring the metabolic activity of the soft tissue adjacent to a fracture site.[12] A radiotracer used in PET scanning of the bone is ^{18}F-labelled sodium fluoride (Na^{18}F, referred to as ^{18}F-PET herein).

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 2) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and fracture.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. The search was also limited to English language documents, with no publication date limits. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

The database/literature search identified 785 citations, from which 44 articles underwent full-text screening. Of these, 29 were included in the final report. No HTAs were identified through the literature review. Two relevant systematic reviews and meta-analyses were identified: one relevant to criteria 2, 3, and 4 was identified through the grey literature search,[13] and the other pertaining to the diagnostic accuracy of bone scintigraphy compared with CT and MRI.[14] No systematic reviews comparing bone scintigraphy and ^{18}F-PET were identified. Six primary studies reporting on diagnostic accuracy were included.

The remaining articles identified through the search, along with articles found through searching the grey literature and from reference lists, were used to abstract information on the rest of the criteria.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	*Osteoporotic fracture* There are an estimated 138,600 osteoporosis-associated fractures each year in Canada.[15] *Stress fracture* The incidence of stress fracture is less than 1% in the general population.[16] Based on this available information, it is estimated that the size of the affected population is: • more than 1 in 1,000 (0.1%) and less than or equal to 1 in 100 (1%) for osteoporosis-associated fracture • more than 1 in 1,000 (0.1%) and less than or equal to 1 in 100 (1%) for stress fracture.
2	**Timeliness and urgency of test results in planning patient management**	*Osteoporotic fracture* Delayed recognition of osteoporotic fractures, particularly in the elderly, can result in progression to complete fracture, resulting in considerable long-term residual disability and mortality. A 2007 study on wait times for fracture management at the MUHC reported that hip fractures should be corrected within 24 hours.[13] *Stress fracture* Delay in diagnosis of stress fractures may result in progression to complete fracture, non-union, delayed union, and need for operative intervention or refracture.[17,18] Based on this information, the target time frame for performing the ^{99m}Tc-based test is: • between 2 and 7 days, and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has a significant impact on the management of the condition or the effective use of heath care resources in adults with suspected osteoporotic fracture • between 8 and 30 days, and obtaining the test results in the appropriate timely manner for the underlying condition has moderate impact on the management of the condition or the effective use of heath care resources in patients with suspected stress fracture.

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	*Osteoporotic fracture* No data on the effect of missed or delayed diagnosis of osteoporosis-related fractures on mortality were identified. However, untreated occult fractures can proceed to a complete fracture, which may affect mortality. A 5-year observational study of Canadians older than 50 years found that compared with participants without fracture, those with hip or vertebral fractures were more likely to die during the 5 years of follow-up.[19] Fractures of the forearm or wrist and ribs had no impact on mortality.[19] *Stress fracture* Stress fracture is not associated with increased risk of death in otherwise healthy adults. Based on the available evidence, it is assumed that diagnostic imaging test results can have: • a moderate impact on the mortality of patients suspected of having osteoporotic fractures • no impact on mortality in cases of suspected stress fracture.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	*Osteoporotic fracture* Fractures resulting from osteoporosis are associated with clinically important functional decline and reduced quality of life. The site of fracture, particularly in the elderly, will affect morbidity. According to the MUHC, early fixation of hip fracture results in reduced pain and disability, easier surgical fixation, reduced OR time, and shorter post-operative stay.[13] Likewise, wrist fractures can affect activities of daily living, such as meal preparation, and cause loss of functional independence.[20] *Stress fracture* Undiagnosed and untreated stress fracture can progress to complete fracture, potentially resulting in significant morbidity and reduced quality of life.[21] Based on the available evidence, it is assumed that diagnostic imaging test results can have a: • significant impact on morbidity or quality of life of patients suspected of having osteoporotic fracture • moderate impact on morbidity or quality of life of patients suspected of having stress fracture.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	*Bone scintigraphy* Patients, or parents of patients, may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent and potential need for sedation.[22] *CT* Patients, or parents of patients, may have concerns about radiation exposure and may also feel claustrophobic while in the scanner, although this may be less of a problem with new CT scanners (MIIMAC expert opinion). *MRI* Patients may experience feelings of claustrophobia or apprehension and be bothered by the noise, although this may be less of a problem with new MRI machines (MIIMAC expert opinion). Some patients may have difficulty remaining still during the scan, and children may require sedation.[23] Patients are not exposed to radiation during a MRI scan, which may be more acceptable to some. *^{18}F-PET* Patients, or parents of patients, may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. Overall, bone scintigraphy with ^{99m}Tc-labelled radiotracers: • has similar acceptability to CT • is minimally less acceptable than MRI • is minimally less acceptable than ^{18}F-PET.

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>A 2010 systematic review compared the diagnostic accuracy of bone scintigraphy with CT and MRI.[14]
<table>
<tr><th colspan="4">Pooled Estimates of Sensitivity and Specificity[14]</th></tr>
<tr><th>Imaging Modality</th><th>Number of Studies (N)</th><th>Sensitivity (95% CI)</th><th>Specificity (95% CI)</th></tr>
<tr><td>Bone scintigraphy</td><td>15 (N = 1,102)</td><td>97% (93% to 99%)</td><td>89% (83% to 94%)</td></tr>
<tr><td>CT</td><td>6 (N = 211)</td><td>93% (83% to 98%)</td><td>99% (96% to 100%)</td></tr>
<tr><td>MRI</td><td>10 (N = 513)</td><td>96% (91% to 99%)</td><td>99% (96% to 100%)</td></tr>
</table>
CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging; N = number of patients.

Five primary studies compared the diagnostic accuracy of bone scintigraphy with MRI for detection of stress fracture.[24-28] Two primary studies compared bone scintigraphy with CT (findings from one study were reported in two separate publications).[29,30] Sensitivity and specificity values were consistent with those reported in the systematic review.

No studies were identified that compared ^{99m}Tc-based imaging with ^{18}F-PET.

Based on the available evidence, the diagnostic accuracy of bone scintigraphy with ^{99m}Tc-labelled radiotracers is:
• similar to CT
• minimally lower than MRI
• similar to ^{18}F-PET.</td></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>Non–radiation-related Risks

Bone scintigraphy
Rare, mild adverse reactions with ^{99m}Tc-labelled tracers (e.g., skin reactions) have been reported.[31-33] Although the MDP radionuclide clears faster in young children with normal kidney function, no additional dosing is generally needed.[34]</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses	
Criterion	**Synthesized Information**

CT

Patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[35] According to the American College of Radiology *Manual on Contrast Media*,[36] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[36]

MRI

MRI is contraindicated in patients with metallic implants, including pacemakers and, potentially, hearing aids.[37] Moderate AEs resembling an allergic reaction to the contrast media (if required) are possible.[36] The frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%) and the frequency of moderate reactions is also rare (0.004% to 0.7%).[36]

PET

The Pharmacopeia Committee of the SNM conducted a 4-year prospective evaluation of PET and reported no AEs among the 33,925 scans conducted in 22 participating PET centres in the United States.[38]

Radiation-related Risks

Patients undergoing bone scintigraphy, CT, and ^{18}F-PET are exposed to ionizing radiation.

Table 3: Effective Doses of Radiation

Procedure	Average Dose (mSv)
^{99m}Tc-labelled tracers bone scan	6.3[39,40]
CT	6 to 25[41,42]
MRI	0[39]
Whole body PET*	14.1[41]
Average background dose of radiation per year	1 to 3.0[43-45]

CT = computed tomography; MRI = magnetic resonance imaging; mSv = millisievert; PET = positron emission tomography; ^{99m}TC = technetium-99m.

*Estimate higher than what people would be exposed to for a single site.

Overall, bone scintigraphy with ^{99m}Tc-labelled radiotracers:

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		• has a similar safety profile to that of CT • is minimally less safe than MRI • has a similar safety profile to that of ^{18}F-PET.
9	**Relative availability of personnel with expertise and experience required for the test**	*Bone scintigraphy* In Canada, physicians involved in the performance, supervision, and interpretation of bone scintigraphy should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[46] Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body. *CT* Medical radiation technologists who are certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. Training of technologists specifically engaged in CT should meet the applicable and valid national and provincial specialty qualifications. *MRI* MRI medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by the CAMRT. *PET* In Canada, physicians involved in the performance, supervision, and interpretation of PET scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging. Technologists must be certified by CAMRT or an equivalent licensing body. Assuming the necessary equipment is available, if bone scintigraphy with ^{99m}Tc-based imaging is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using CT • 75% to 94% of the procedures can be performed in a timely manner using MRI • fewer than 25% of the procedures can be performed in a timely manner using PET.
10	**Accessibility of**	*Bone scintigraphy*

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td>alternative tests (equipment and wait times)</td><td>Nuclear medicine facilities with gamma cameras (including SPECT) are required. No nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[47]

CT
There are no CT scanners available in Nunavut.[47] For CT scanners, the average weekly use ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[12] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[48]

MRI
There are no MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[47] According to CIHI’s National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006-2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario, with a national average of 71 hours.[12] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[48]

PET
A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[49] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[49] There are 36 PET or PET/CT scanners, 4 of which are used for research purposes only.[49]

Assuming the availability of personnel with the necessary expertise and experience, if ^{99m}Tc-based bone scintigraphy is not available, it is estimated that:
more than 95% of the procedures can be performed in a timely manner using CT
75% to 94% of the procedures can be performed in a timely manner using MRI
fewer than 25% of the procedures can be performed in a timely manner using PET.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of a bone scan with ^{99m}Tc-based radioisotopes is $335.55. CT and MRI are minimally more costly alternatives and ^{18}F-PET is a significantly more costly alternative.

<table><tr><th colspan="3">Relative Costs</th></tr><tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr></table></td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses					
Criterion		**Synthesized Information**			
		Bone scan	335.55	Reference	
		CT	262.56	–72.99	
		MRI	501.90	+166.35	
		^{18}F-PET	850.00	+514.45	

AE = adverse events; CI = confidence interval; CIHI = Canadian Institute for Health Information; CT = computed tomography; ^{18}FDG = 18F-fluorodeoxyglucose; Gd = gadolinium; MDP = methylene diphosphonate; MR = magnetic resonance; MRI = magnetic resonance imaging; MUHC = McGill University Health Centre; OR = operating room;; PET = positron emission tomography; SNM = Society of Nuclear Medicine; SPECT = single-photon emission computer tomography; ^{99m}Tc = technetium-99.

CRITERION 1: Size of affected population (link to definition)

The potential adult population requiring bone scintigraphy is primarily Canadians with stress fractures and elderly persons with osteoporosis (most common cause of fracture in the elderly).[50]

Osteoporotic fracture
Osteoporosis is a skeletal disease characterized by low bone mass and deterioration of bone tissue, leading to increased susceptibility to fracture.[50,51] Although diagnosis is usually made with standard x-ray, fracture may not be apparent on radiography, and occult fractures are estimated to occur in 2% to 9% of patients.[52]

There are an estimated 138,600 osteoporosis-associated fractures each year in Canada.[15] Estimates from Saskatchewan indicate that 8.5 per 1,000 women and 4.4 per 1,000 men between the ages of 75 and 84 break their hip. Over the age of 85 years, this increases to 22.5 per 1,000 for women and 14.1 per 1,000 for men.[53]

Stress fracture
The available literature suggests that stress fractures are common injuries in athletes (professional and recreational), dancers, and military recruits. Track and field athletes have the highest reported incidence of stress fractures compared with other athletes.[2] The most common affected bones for stress fractures are in the lower extremity (tibia, metatarsals, and fibula)[2] and hip (e.g., femoral neck);[54] however, they can also occur in non–weight-bearing bones such as ribs, upper extremities, or pelvis.[55]

In the military, stress fractures of the calcaneus bone are also reported to be common.[2] Epidemiological research demonstrates that risk factors for stress fracture include prior stress fracture, status of physical fitness, physical activity, and gender.[16]

Women are at a greater risk of stress fractures, with a reported relative risk ranging from 1.2 to 10.[16] Tibial fractures are most common in athletes and military recruits (38.2% to 51.2%), followed by femoral neck fractures (29.8%) and fractures of the foot (i.e., tarsal or tarsal navicular fracture [11.8% to 25.3%]).[16] Stress fractures within the metatarsals (8.8% to 20.6%) and femur (7.2% to 20.6%) occur at similar rates.[54,56]

In general, stress fractures occur in less than 1% of the general population.[16] In a civilian athletic population, 10% of injuries experienced are stress fractures,[54,57,58] while female and male athletes report having stress fractures at 13% and 8%, respectively.[54] Military recruits have reported incidence of fracture from as low as 1% to as high as 31%, depending on the number of weeks within training.[55]

Return to Summary Table

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Failure to diagnose occult or hidden fracture, including stress fracture, can result in progression to complete fracture of a previously non-displaced fracture, which can lead to subsequent long-term residual disability and morbidity. Potential complications, including non-union, avascular necrosis, and osteoarthritis, are made more likely by a delay in diagnosis and treatment. Hence, prompt identification and treatment of occult fractures are critical for improving outcomes.

Osteoporotic fracture
In the elderly, delayed recognition of osteoporotic fractures can result in considerable long-term residual disability and mortality. This is especially true as occurrence of fragility fracture increases the risk of further fractures, highlighting the need for prompt detection of fracture and appropriate therapy to decrease the risk of future fractures.[59] When hip fracture is detected early, appropriate treatment can minimize morbidity and mortality and prevent the rapid decline in quality of life that is often associated with this injury.[60] A 2007 systematic review on wait times for fracture management at the McGill University Health Centre (MUHC) reported that expert opinion and guidelines unanimously concluded that hip fractures should be corrected within 24 hours in the absence of medical contraindications.[13] Early fixation results in reduced pain and disability, easier surgical fixation, reduced operating room (OR) time, and shorter post-operative stay.[13]

Stress fracture
A delay in the diagnosis of high-risk stress fractures may result in progression to a complete fracture, non-union, delayed union, need for operative intervention, or refracture.[17,18] For example, early diagnosis is quite important for fractures of the tarsal navicular, as complications are high, and early recognition of partial fracture damage can be confined to the dorsal portion to prevent complete fracture.[61] Therefore, early diagnosis of stress fractures assists in reducing morbidity.[7,18]

Return to Summary Table

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Osteoporotic fracture
Persons with hip or vertebral fractures have substantially increased risk of death after fracture.[62] Osteoporosis Canada reports that up to 30% of cases of hip fracture induced by osteoporosis result in death, and an estimated 23% of patients with hip fracture die in less than year.[50] Although men are less likely than women to have osteoporosis, they have higher post-fracture mortality and institutionalization rates than women.[62]

A recent report by Ioannidis et al. reported on the relation between fractures and mortality in the Canadian Multicentre Osteoporosis Study.[19] The five-year observational study compared incidence of fracture and mortality in a cohort of 7,753 people (2,187 men and 5,566 women) aged 50 years and older in Canada. Results demonstrated that compared with participants without fracture, those with hip or vertebral fractures were more likely to die during the five years of follow-up (adjusted hazard ratio [HR] 2.7, 95% confidence interval [CI] 1.1 to 6.6 for vertebral fracture; HR 3.2, 95% CI 1.4 to 7.4 for hip fracture). Fractures of the forearm or wrist and ribs had no impact on mortality.[19]

Stress fracture
It is not likely that accidental occult skeletal fracture alone will affect mortality in otherwise healthy adults.

Return to Summary Table

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Osteoporotic fracture
Fractures, particularly in the elderly, are associated with significant morbidity and reduced quality of life. Recent evidence-based guidelines report that delay in hip fracture treatment results in increased length of hospital stay and more complications, including pressure sores, pneumonia, and confusion.[63] A 2007 systematic review by MUHC concluded that early fixation of hip fracture results in reduced pain and disability, easier surgical fixation, reduced OR time, and shorter post-operative stay.[13]

Wrist fractures are associated with clinically important functional decline and reduced quality of life in older women with respect to activities of daily living, such as meal preparation, and may cause loss of functional independence.[20]

Stress fracture
Stress fractures, if not diagnosed and treated promptly, can progress to complete fracture, potentially resulting in significant morbidity. Potential complications include delayed union, need for operative intervention, refracture, avascular necrosis, and osteoarthritis,[17,18] which may impede the patient's return to activity.[21]

Return to Summary Table

CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

No information was found on the potential health disparities relating specifically to the detection of osteoporotic or stress fracture.

Women are at greater risk for stress- and osteoporosis-induced fracture. Risk of osteoporosis and, subsequently, fracture increases with age, regardless of ethnicity.[59,64] Wrist fractures are more common in women younger than 75 years, whereas hip fractures become more common in women older than 75 years.[20] Although osteoporosis is less common in men than in women, elderly men account for almost 30% of hip fracture cases. Men also have higher post-fracture mortality and institutionalization rates than women.[62]

A Saskatchewan study found that in Manitoba First Nations elderly, the rate of osteoporotic fracture at all sites was nearly double that of age- and sex-matched non-Aboriginal controls (6.3 versus 3.0 per 1,000 person years), regardless of diabetes diagnosis.[65]

Return to Summary Table

CRITERION 6: Relative acceptability of the test to patients (link to definition)

Bone scintigraphy
Limited information was identified on the acceptability of bone scintigraphy to patients. A retrospective study on the use of bone scintigraphy in children with osteosarcoma or Ewing sarcoma suggested that any test, including a bone scintigraphy, causes psychological strain on the children and the parents.[66] Patients, or parents of patients, may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

CT
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This may be less of a problem with new CT scanners, if available (MIIMAC expert opinion). Patients may also be required to hold their breath for a substantial period of time, which is seen as "uncomfortable" and "difficult."[67]

MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[68,69] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

PET
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

Return to Summary Table

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

A literature search was conducted to evaluate the diagnostic accuracy of bone scintigraphy relative to the alternative diagnostic tests. One relevant systematic review/meta-analysis[14] and seven primary studies not included in the systematic review compared the diagnostic performance and accuracy of bone scintigraphy with MRI, CT, or PET for diagnosis of fractures. The primary studies were heterogeneous in terms of study design, target population, site of fracture, comparators, and reported outcome measures. The identified studies are described below and the results of each study are summarized in Appendix 4. No studies were identified that compared ^{99m}Tc-based imaging with ^{18}F-PET.

Systematic reviews

Bone scintigraphy versus CT
One 2010 systematic review and meta-analysis compared the diagnostic performance and accuracy of bone scintigraphy, MRI, and CT for diagnosis of suspected scaphoid fractures.[14] Twenty-six studies were identified between January 1966 and October 2008. Pooled sensitivity, specificity, the diagnostic odds ratio (DOR), were calculated and presented in Table 2. There was no difference in DOR between CT and bone scintigraphy (P = 0.12). The positive and negative likelihood ratios derived from the pooled sensitivities and specificities were 93 and 0.07, respectively, for CT, compared with 8.82 and 0.03 for bone scintigraphy. As a general rule, positive likelihood ratios greater than 10 and negative likelihood ratios less than 0.1 are considered to provide strong evidence to rule in or rule out diagnoses.[14] The authors conclude that additional studies are needed to assess the diagnostic performance of CT compared with bone scintigraphy.[14]

Table 2: Pooled Estimates of Sensitivity, Specificity, and DOR[14]

Imaging Modality	Number of Studies (N)	Sensitivity (95% CI)	Specificity (95% CI)	DOR (95% CI)
Bone scintigraphy	15 (N = 1,102)	97% (93% to 99%)	89% (83% to 94%)	4.78 (4.02 to 5.54)
CT	6 (N = 211)	93% (83% to 98%)	99% (96% to 100%)	6.11 (4.56 to 7.76)
MRI	10 (N = 513)	96% (91% to 99%)	99% (96% to 100%)	6.60 (5.43 to 7.76)

CI = confidence interval; DOR = diagnostic odds ratio; MRI = magnetic resonance imaging;[14] N = number of patients.

Bone scintigraphy versus MRI

The Yin et al. systematic review and meta-analysis compared the diagnostic accuracy of bone scintigraphy with MRI for diagnosing scaphoid fracture (Table 2).[14] Pooled sensitivity, specificity, and DOR for bone scintigraphy and MRI are presented in Table 2. The positive likelihood ratios of MRI were greater than 90 (i.e., 96) and negative likelihood ratio less than 0.1 (i.e., 0.04). The authors conclude that bone scintigraphy and MRI have equally high sensitivity and high diagnostic value for excluding scaphoid fracture; however, MRI is more specific and better for confirming scaphoid fracture.[14]

In 2005, Foex and colleagues[70] published results of a "shortcut review" to establish whether MRI or bone scintigraphy is better at identifying scaphoid fractures not apparent on plain x-rays. They identified four applicable studies dated from 1966 to March 2005, which included 145 patients and compared the two imaging modalities. Although the sensitivity and specificity were not calculated, the results suggested that MRI is slightly superior to bone scintigraphy in the diagnosis of occult scaphoid fractures. MRI also allows for accurate diagnosis of clinically significant soft tissue injuries, which might otherwise be missed. MRI was also quicker to perform than bone scintigraphy. The authors concluded that (1) MRI is the investigation of choice in clinically suspected scaphoid fracture after negative initial and 10- to 14-day follow-up x-rays, and (2) bone scintigraphy is a reasonable alternative in patients with claustrophobia.[70]

Primary studies

Bone scintigraphy versus multiple alternatives

Gaeta et al.[24]

In this prospective study (January 2001 to November 2003), the diagnostic accuracy of MRI, CT, and bone scintigraphy were compared in 42 recreational athletes with suspected tibial stress injury (mean age: 28.2 years, range: 16 to 37 years) and 10 asymptomatic controls. All patients underwent initial radiography that was negative for injury. Sensitivity of MRI, CT, and bone scintigraphy was 88%, 42%, and 74%, respectively. Specificity, accuracy, and positive and negative predictive values were 100%, 90%, 100%, and 62%, respectively, for MRI and 100%, 52%, 100%, and 26%, respectively, for CT. Significant difference in detection of early tibial stress injuries was found between MRI and both CT and bone scintigraphy (McNemar test; $P < 0.001$; $P = 0.008$, respectively). The authors conclude that MRI is the single best technique to assess patients with suspected tibial stress injury; CT can detect osteopenia in some patients with negative MRI findings.

Bone scintigraphy versus CT

Groves et al.[29,30] (findings from one study were reported in two separate publications)

In this prospective study, 16-detector CT was compared with bone scintigraphy in 26 patients with suspected stress fracture (a total of 33 suspected fractures). Bone scintigraphy identified 13 of 33 cases of stress fracture, whereas CT identified only four cases. There were eight "scintigraphy positive–CT negative" discordant cases. CT demonstrated more details of bone cortex and trabecular compared with bone scintigraphy. The authors concluded that multi-section CT cannot be recommended as a first-line diagnostic tool for stress fractures. They suggested that CT should be reserved for special circumstances, such as uncertain result of bone scintigraphy or to rule out other differential diagnoses.

Bone scintigraphy versus MRI

Ishibashi et al.[26]
In this prospective study, radiography, scintigraphy, and MRI were compared in 31 patients with suspected stress injuries of the bone. Even with negative initial radiographic findings, initial scintigraphy and MRI indicated stress injury, although MRI showed more diagnostic information (e.g., fracture line and periosteal edema) compared with bone scintigraphy. The authors conclude that compared with bone scintigraphy, MRI is less invasive and provides more information and is recommended for initial diagnosis of suspected stress injury to bone.

Kiuru et al.[27]
In this retrospective chart review, the accuracy of radiography and MRI was compared with bone scintigraphy, as a gold standard, in 50 military trainees with stress-related pain in the pelvis or lower extremities. Bone scintigraphy was performed within an average of 14 days from the radiography, and MRI performed within two days after bone scintigraphy. Sensitivity, specificity, and positive and negative predictive values were reported to be 56%, 94%, 95%, and 48%, respectively, for radiography (accuracy 67%) and 100%, 86%, 93%, and 100%, respectively, for MRI (accuracy 95%). The authors suggested that MRI is more sensitive than bone scintigraphy and this technique should be used as the standard of reference in the assessment of stress injuries of bone.

Hodler et al.[25]
In this study, the diagnostic accuracy of MRI was compared with that of bone scintigraphy in 16 patients with normal radiography results and typical bone scintigraphy results suggestive of stress-related bone injuries. Standard of reference consisted of a combination of clinical and scintigraphic findings and clinical follow-up. Bone scintigraphy was reported to correctly identify all normal and abnormal findings. The accuracy measurements reported by two independent readers differed (intra-observer agreement = 0.62). For MRI, the two readers reported the sensitivity, specificity, and positive and negative predictive values to be 69%/63%, 100%/80%, 100%/91%, and 50%/40%, respectively. The authors concluded that bone scintigraphy should be considered as the initial imaging modality in patients with clinically suspected stress-related injuries for whom the probability of other active bone diseases, such as infection or cancer, is low.

Shin et al.[28]
In this prospective study, the accuracy of MRI and bone scintigraphy was compared in differentiating the cause of hip pain. Nineteen military members who were engaged in endurance training and had hip pain (a total of 22 hips) were included. The patients underwent bone scintigraphy (imaged in plantar and SPECT modes). MRI of both hips was also performed for the patients who had bone scintigraphy results suggestive of femoral neck stress fracture. The diagnosis was confirmed with a follow-up x-ray examination and clinical evaluation six weeks after the MRI scan. Bone scintigraphy had an accuracy of 68% for detection of femoral

neck stress fractures, whereas MRI was 100% accurate. The authors concluded that MRI was superior to bone scintigraphy in differentiating the causes of hip pain in endurance athletes.

Bone scintigraphy versus PET
^{18}F-PET is increasingly being used for evaluation of skeletal trauma;[71] however, no studies were identified that compared the diagnostic accuracy of ^{18}F-PET with bone scintigraphy for this indication.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Bone scintigraphy
Several studies[31-33,72] reported mild adverse events with ^{99m}Tc-labelled tracers (e.g., skin reactions) and one case report published in 1985 reported a patient who experienced a rash following two bone scintigraphy procedures with ^{99m}Tc-MDP, one in 1983 and one the following year.[73] The authors concluded that this patient had an allergic reaction to MDP on both occasions. This case report references an older study that reported 22 adverse reactions to ^{99m}Tc-MDP, in which 20 of the reactions were either “probably” or “possibly” caused by MDP.

CT
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[35] In addition, patients may experience mild side effects from the contrast agent, such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and Gd contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[74] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. Specifically, Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[36] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[36]

MRI
MRI is contraindicated in patients with metallic implants, including pacemakers.[37] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[35] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[36] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[36]

PET
The Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year

prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[38]

Radiation-related Risks

Among the modalities to diagnose fractures, bone scintigraphy and ^{18}F-PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 3. It should be noted that the estimate for PET is higher than what a patient would be exposed to for a single site scan.

Table 3: Effective Doses of Radiation[41,42]

Procedure	Average Effective Dose (mSv)
^{99m}Tc-labelled tracers bone scan	6.3
CT	6 to 25
Whole body PET	14.1
MRI	0
Average background dose of radiation per year	1 to 3.0[43-45]

CT = computed tomography; MRI = magnetic resonance imaging; mSv = millisievert, PET = positron emission tomography; ^{99m}Tc = technetium-99m.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to diagnose occult fractures are presented by imaging modality. A summary of the availability of personnel required to diagnose fractures, by bone scintigraphy or any of the alternative imaging modalities, is provided in Table 4.

Bone scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of bone scintigraphy should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[46] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct bone scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound should be diagnostic radiologists[12] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[46]

Medical radiation technologists (MRTs) must be certified by CAMRT or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on-site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[46]

CT
For the performance of CT scan, MRTs who are certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists specifically engaged in CT should meet the applicable and valid national and provincial specialty qualifications.

MRI
For the performance of MRI, medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

PET
In Canada, physicians involved in the performance, supervision, and interpretation of PET scans should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Technologists must be certified by CAMRT or an equivalent licensing body.

Table 4: Medical Imaging Professionals in Canada[12]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	Medical Radiation Technologists	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdictions; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; ON = Ontario; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
*This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 5 provides an overview of the availability of equipment required to diagnose fracture. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010.

Table 5: Diagnostic Imaging Equipment in Canada[12,47,49]

	Nuclear Medicine Cameras	CT Scanners	MRI Scanners	SPECT/CT Scanners	PET or PET/CT scanners
Number of devices	603[12]	460[47]	218[47]	96[47]	36[49]
Average number of hours of operation per week (2006-2007)	40	60	71	n/a	n/a
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	PEI, YT, NT, NU	NL, PEI, SK, YT, NT, NU

CT = computed tomography; MRI = magnetic resonance imaging; n/a = not applicable; NL = Newfoundland and Labrador; NU = Nunavut; NT = Northwest Territories; PEI = Prince Edward Island; PET = positron emission tomography; SK = Saskatchewan; SPECT = single-photon emission computed tomography; YT = Yukon.

Bone scintigraphy

For bone scintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[12]

CT

No CT scanners are available in Nunavut.[12] The average weekly use of CT scanners ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[12] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[48]

MRI

No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[12] According to the Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006-2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario, with a national average of 71 hours.[12] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[48]

PET

A 2010 Environmental Scan published by CADTH reported that approximately 31 Canadian centres are equipped to perform PET scans.[49] These centres are located in the provinces of: British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[49] There are 36 PET or PET/CT scanners, four of which are used for research purposes only.[49]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of bone scanning and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical and surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 6), the cost of a bone scan with ^{99m}Tc-based radioisotopes is $335.55. CT and MRI are minimally more costly alternatives and ^{18}F-PET is a significantly more costly alternative.

Table 6: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[75]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
Bone scan				
J867	Blood flow and pool imaging	58.75	29.30	88.05
J851	Bone scintigraphy — single site	87.00	50.95	137.95
J866	Application of tomography (SPECT)	44.60	31.10	75.70
Maintenance fees — global budget		33.85		33.85
	TOTAL	224.20	111.35	**335.55**
CT				
X231	CT — pelvis — without IV contrast		91.15	91.15
Technical cost — from global budget		150.00		150.00
Maintenance fees — from global budget		21.41		21.41
	TOTAL	171.41	91.15	**262.56**
MRI				
X471C	Multislice sequence, one extremity and/or one joint		66.10	66.10
X475C (×3)	Repeat (another plane, different pulse sequence; to a maximum of 3 repeats)		33.10 (×3) = 99.30	99.30
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		36.50		36.50
	TOTAL	336.50	165.40	**501.90**
^{18}F-PET				
Professional fee for PET			250.00	250.00
Technical cost — from global budget		600.00		600.00
	TOTAL	800.00	250.00	**850.00**

CT = computed tomography; ^{18}F-PET = 18F-labelled fluoride position emission tomography; IV = intravenous; MRI = magnetic resonance imaging; prof. = professional; SPECT = single-photon emission computed tomography; tech. = technical.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the technetium-99m (^{99m}Tc)-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Database(s): EBM Reviews - ACP Journal Club 1991 to February 2011 EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011 EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 2011 EBM Reviews - Cochrane Methodology Register 1st Quarter 2011 EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2011 EBM Reviews - Health Technology Assessment 1st Quarter 2011 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to March 16, 2011 **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	March 16, 2011
Alerts:	Monthly search updates began January 14, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	English language 2001-2011 for primary studies Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Multi-database Strategy	
#	**Searches**
1	exp Fractures, Bone/
2	Fractur*.ti,ab.
3	((bone or bones or bony or boney or scull or limb or skeleton* or skeletal* or arm or arms or leg or legs or jaw or jaws or joint or joints or spine* or spinal or rib or ribs or pelvis or pelvic or foot or feet or ankle* or clavicle* or shoulder* or hip or hips or femur* or femoral* or humeral* or humerus or hand or hands or finger* or nose or nasal or wrist* or knee or knees or face or occipital or tibia or ulna or intra-articular* or intraarticular* or osteoporotic* or peri-prosthetic* or periprosthetic* or maxilla* or mandibular or skull or cranial or metacarpal or metatarsal or sternal or scapular or vertebral) adj2 (broken or break or breakage or crack*)).ti,ab.
4	or/1-3
5	Technetium/ or exp Technetium Compounds/ or exp Organotechnetium Compounds/ or exp Radiopharmaceuticals/
6	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.
7	Radionuclide Imaging/ or Perfusion Imaging/
8	radionuclide imaging.fs.
9	radioisotope*.mp.
10	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
11	Tomography, Emission-Computed, Single-Photon/
12	(single-photon adj2 emission*).ti,ab.
13	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
14	(medronate or methyl diphosphonate).ti,ab.
15	exp Child abuse/ri
16	exp "Bone and Bones"/ri
17	or/5-16
18	4 and 17
19	(fracture* adj2 (scan* or imag*)).ti,ab.
20	18 or 19
21	(child or children or infant* or baby or babies or newborn* or neonate or neonates or neonatal or preemie or preemies or paediatric* or pediatric* or toddler* or girl or girls or boy or boys or kid or kids).ti,ab.
22	(abuse or abusive or abused).ti,ab.
23	17 and 21 and 22
24	20 or 23
25	meta-analysis.pt.
26	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
27	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
28	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
29	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
30	(data synthes* or data extraction* or data abstraction*).ti,ab.
31	(handsearch* or hand search*).ti,ab.
32	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
33	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.

Multi-database Strategy	
34	(meta regression* or metaregression* or mega regression*).ti,ab.
35	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
36	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
37	(cochrane or health technology assessment or evidence report).jw.
38	(meta-analysis or systematic review).md.
39	or/25-38
40	24 and 39
41	exp "Sensitivity and Specificity"/
42	False Positive Reactions/
43	False Negative Reactions/
44	du.fs.
45	sensitivit*.tw.
46	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti,ab.
47	(predictive adj4 value*).tw.
48	Comparative Study.pt.
49	(Validation Studies or Evaluation Studies).pt.
50	Randomized Controlled Trial.pt.
51	Controlled Clinical Trial.pt.
52	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
53	Multicenter Study.pt.
54	(random* or sham or placebo*).ti.
55	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
56	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
57	(control* adj3 (study or studies or trial*)).ti.
58	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
59	(allocated adj "to").ti.
60	Cohort Studies/
61	Longitudinal Studies/
62	Prospective Studies/
63	Follow-Up Studies/
64	Retrospective Studies/
65	Case-Control Studies/
66	Cross-Sectional Study/
67	(observational adj3 (study or studies or design or analysis or analyses)).ti.
68	cohort.ti.
69	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
70	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
71	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
72	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
73	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
74	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
75	(population adj3 (study or studies or analysis or analyses)).ti.
76	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
77	or/41-76

Multi-database Strategy	
78	77 not case reports.pt.
79	24 and 78
80	exp animals/
81	exp animal experimentation/
82	exp models animal/
83	exp animal experiment/
84	nonhuman/
85	exp vertebrate/
86	animal.po.
87	or/80-86
88	exp humans/
89	exp human experiment/
90	human.po.
91	or/88-90
92	87 not 91
93	79 not 92

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	March 2011
Keywords:	Fractures (including child abuse) and radionuclide imaging
Limits:	English language Human limits for primary studies

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters), were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Definitions

Diaphysis: The main or midsection (shaft) of a long bone. It is made up of cortical bone and usually contains bone marrow and adipose tissue (fat).

Occult: A fracture that does not appear in x-rays, although the bone shows new bone formation within three or four weeks of fracture.

Appendix 4: Diagnostic Accuracy

Table 7: Diagnostic Accuracy of Bone Scintigraphy and Alternative Tests							
Author(s), Year, Country	**Study Design**	**Population/ Condition**	**Diagnostic Accuracy of Tests (%)**				**Standard of Reference**
			Bone Scintigraphy	**CT**	**MRI**	**PET**	
Systematic review/Meta-analysis							
Yin et al. 2009[14] China	Systematic review and meta-analysis	26 studies (N = 1,826) assessing the diagnostic performance of bone scintigraphy, CT, and MRI for detection of scaphoid fracture (age range, 22 to 44 years) included.	Sens: 97% (95% CI, 93 to 99) Spec: 89% (95% CI, 83 to 94)	Sens: 93% (95% CI, 83 to 98) Spec: 99% (95% CI, 96 to 100)	Sens: 96% (95% CI, 91 to 99) Spec: 99% (95% CI, 96 to 100)		Follow-up images (radiographs, CT, MRI, or bone scintigraphy) or clinical follow-up and/or combined images
Primary studies							
Gaeta et al. 2005[24] Italy	Prospective observational	42 athletes (mean age: 28.2 years; age range 16 to 37 years) with occult tibial stress injury	Sens: 74% Spec: NR PPV: NR NPV: NR	Sens: 42% Spec: 100% PPV: 52% NPV: 100%	Sens: 88% Spec: 100% PPV: 90% NPV: 100%		Review of clinical findings, physical exam, and detailed history by 3 sports medicine physicians
Groves et al. 2005[29,30] UK	Prospective observational	Military recruits with lower limb stress-related symptoms (33 suspected stress fractures in 26 patients) (mean		Sens: 31% Spec: 100% PPV: 52% NPV: 100%			Bone scintigraphy

Table 7: Diagnostic Accuracy of Bone Scintigraphy and Alternative Tests							
Author(s), Year, Country	**Study Design**	**Population/ Condition**	**Diagnostic Accuracy of Tests (%)**				**Standard of Reference**
			Bone Scintigraphy	**CT**	**MRI**	**PET**	
		age: 25 years, range,16 to 67 years)					
Hodler et al. 1998[25] Switzerland	Prospective observational	16 consecutive patients with stress-related injuries	Sens: 100% Spec: 100% PPV: NR NPV: NR		Sens: 63% to 69% Spec: NR PPV: 91% to 100% NPV: 40% to 50%		Clinical and scintigraphic findings plus clinical follow-up
Ishibashi et al. 2002[27] Japan	Prospective observational	Stress injuries (36 extremities) in 31 athletes (mean age: 14.9 years, range 12 to 21 years)	Sens: 86%				MRI
Kiur et al. 2002[27] Finland	Retrospective observational	Military trainees with 41 stress injuries of pelvis or lower extremity in 26 patients			Sens: 100% Spec: 86% PPV: 93% NPV: 100% Acc: 95%		Bone scintigraphy Kappa value for MRI and bone scintigraphy = 0.89
Shin et al. 1996[28] USA	Prospective observational	19 military trainees with hip pain with positive bone scintigraphy	Sens: 100% Spec: NR PPV: 68% NPV: NR				MRI

Acc = accuracy; CI = confidence interval; CT = computed tomography; MRI = magnetic resonance imaging; NPV = negative predictive value; NR = not reported; ^{18}F-PET = sodium fluoride positron emission tomography; PPV = positive predictive value; Sens = sensitivity; Spec = specificity.

Appendix 5: Accidental Fractures in Children

Patient population: Children with accidental fracture.

Comparators: CT, MRI.

CRITERION 1: Size of affected population (link to definition)

Occult accidental pediatric fracture can result from a myriad of reasons, including accidental fall or stress fracture resulting from participation in a recreational activity.

An estimate of the potential pediatric population requiring bone scintigraphy to diagnose occult fracture was derived from a 2009 Canadian prospective study that reported that there were 44 playground-related fractures in 15,074 elementary students attending Toronto schools in 2008.[76] In 2008, Sankor et al. reported that 18% of acute ankle trauma cases in children presenting to the emergency room of a large tertiary care children's hospital in California were occult fractures.[76]

Considering these studies, and assuming the situation is similar in Canada, we estimate the size of the Canadian pediatric population requiring bone scintigraphy for detection of accidental occult fracture to be eight (18% × 44) per 15,074 children (0.05%).

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Prompt diagnosis of fracture in children can prevent onset of potential complications, including non-union, avascular necrosis, and osteoarthritis.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

It is unlikely that accidental occult skeletal fracture alone will affect mortality in children.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Unidentified fractures in children can cause prolonged disability, including limited physical mobility and persistent pain. If untreated, unidentified fracture can progress to complete fracture, potentially having an impact on morbidity and quality of life in affected children.

CRITERION 5: Relative impact on health disparities (link to definition)

No information was found on the potential health disparities relating to the detection of occult accidental fracture in children.

CRITERIA 6–11

PET is not considered an alternate imaging test for diagnosing accidental fracture in children. Additional articles specific to accidental fracture in children were not identified. Hence, Criteria 6 to 11 are as reported for adults.

APPENDIX 2.5

INDICATION OVERVIEW

Osteomyelitis is an infection localized to the bone, most commonly due to the bacterium *Staphylococcus aureus (S. aureus),*[1,2] occurring when infection spreads from soft tissues of joints to bone tissue (i.e., contiguous spread), as a result of direct implantation of an infectious agent to bone during surgery or penetrating trauma or due to direct deposits from the blood stream (hematogenous seeding).[3] Osteomyelitis is a progressive infection and can be divided into an acute or subacute stage, progressing to a chronic stage if left untreated (i.e., inflammatory destruction, necrosis, and bone deformation).[4] Differentiation between acute and chronic osteomyelitis is associated with the timing of disease onset (i.e., injury or presence of infection). A diagnosis of acute osteomyelitis is made when the disease has been discovered within two weeks after initial onset, while chronic osteomyelitis refers to disease that has existed for several months at the time of diagnosis.[5] Management primarily includes early treatment with antimicrobial therapy.[5] Orthopedic surgery (e.g., debridement) may be required in some cases (e.g., complicated penetrating trauma or chronic non-resolving or unresponsive to antibiotic therapy osteomyelitis).

Osteomyelitis occurs in both children and adults and in various subpopulations, including in people with prostheses, diabetes, HIV and AIDS, and sickle-cell disease (SCD), and in athletes.[2,6-15] Common sites of infection include the skull, hip (pelvis, sacroiliac joints, hip joints, and proximal femur), spine, and lower extremities (e.g., knee).[5,16,17] Foot osteomyelitis, often referred to as “pedal osteomyelitis” or “diabetic foot,” is most common in diabetic patients.[18]

The most common method of diagnosing osteomyelitis involves sampling the infected tissue either through bone biopsy or surgery and having laboratory procedures to confirm the existence of bacterial involvement. This is a relatively invasive and costly procedure and there has been an effort to explore alternate non-invasive techniques, including diagnostic imaging, for identifying the presence of infection.[19] Nuclear bone scintigraphy is a frequently performed nuclear medicine procedure for the detection of bone disorders.[20,21]

Population: Adults and children presenting with symptoms consistent with acute osteomyelitis, which include bone pain, tenderness, lower extremity warmth, and swelling.[22]

Intervention: Bone scintigraphy (bone scan).

Bone scintigraphy is a common method used to diagnose acute osteomyelitis.[20,21] Most bone scintigraphs are conducted with the administration of methylene diphosphonate labelled with technetium-99m (^{99m}Tc-MDP).[13] After the radioisotope has been injected into the blood, it accumulates in the bone.[13] Imaging usually occurs in three phases — the first phase (called the angiographic phase) is obtained at the time of administration of ^{99m}Tc-MDP; the second phase, or blood pool phase, is obtained in the first few minutes after injection to assess alterations in vasculature due to inflammation; and the third phase is obtained three to six hours after injection, to look at bone uptake. Images are acquired with a nuclear medicine gamma camera. Early images are usually static (e.g., planar images) but the delayed bone or skeletal images

can be taken as planar or multi-planar cross-sectional single-photon emission computed tomography (SPECT) or SPECT/CT (computed tomography) images (i.e., images like a conventional CT with the bone scan findings incorporated into the CT images — referred to as hybrid imaging), and the diagnosis is determined by the accumulation of the radioactive tracer.[5] Radiotracer accumulates in relatively greater amounts in areas of bone turnover and where there is osteoblast activity, indicative of new bone formation.[23] Ischemia, which is common in osteomyelitis, can prevent the isotopes from collecting and can lead to false-negative results.

Comparators: For this report, the following diagnostic tests are considered as alternatives to bone scintigraphy with ^{99m}Tc:

- *Computed Tomography (CT)*
- *Leukocyte Indium-111 White Blood Cell Scan (^{111}In-WBC)*
- *Magnetic Resonance Imaging (MRI)*
- *18F-fluorodeoxyglucose Positron Emission Tomography (^{18}FDG-PET)*
- *Ultrasound (U/S)*

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and osteomyelitis.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. No date or human limits were applied to the HTA/SR/MA search. For primary studies, the retrieval was limited to documents published between January 1, 2006, and February 18, 2011, and the human population. Both searches were also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

Twenty potential clinical articles were identified through the HTA/SR/MA filtered search and 18 were subjected to full text review. One hundred and seventy-four potential primary studies were identified with a search of primary studies. Additional studies were identified in searches for grey literature, targeted searches, and alerts.

This review focused on acute osteomyelitis; however, studies that did not explicitly state that the osteomyelitis was acute were included in this report. Studies that were solely based on chronic osteomyelitis were excluded.

Information from two meta-analyses,[24,25] one systematic review,[26] and one primary study[27] was used to inform criterion 7 on diagnostic accuracy. For the other criteria, included studies were not limited by study design or date, and were obtained from the HTA/SR/MA search, the primary studies search, grey literature searching, targeted searching, and handsearching.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	**Adult acute osteomyelitis** Osteomyelitis affects 1 in every 10,000 people worldwide.[1] Assuming this incidence rate applies to Canada, the estimated size of the population is 0.01%. **Pediatric acute osteomyelitis** 13 in 10,000 children experience acute osteomyelitis in the US.[2] Assuming the incidence rate in Canada is similar to that in the US, this corresponds to more than 1 in 1,000 (0.1%) and less than or equal 1 in 100 (1%) children. The estimated size of the affected adult population is more than 1 in 10,000 (0.01%) and less than or equal to 1 in 1,000 (0.1%). The estimated size of the affected pediatric population is more than 1 in 1,000 (0.1%) and less than 1 in 100 (1%).
2	**Timeliness and urgency of test results in planning patient management**	**Adult and pediatric acute osteomyelitis** The priority for bone scintigraphy in suspected osteomyelitis is 2 to 7 days from the time and date on which the request for an examination is received by the imaging department to the date on which the examination is performed (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). In children, imaging results have a significant impact on the management of the condition or the effective use of health care resources and in adults, the impact is moderate.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	**Adult acute osteomyelitis** Undiagnosed osteomyelitis can lead to septicemia[28] and, in rare cases, death.[29] Statistics Canada reports that in 2007, 83 patients died from osteomyelitis. **Pediatric acute osteomyelitis** Although infections are one of the main causes of death in children, the amount attributed to osteomyelitis is unknown.[6] Diagnostic imaging tests for osteomyelitis would have no impact on mortality in both the adult and pediatric populations

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	**Adult and pediatric acute osteomyelitis** If left untreated, osteomyelitis infection can become chronic and cause a loss of blood supply to the affected bone, leading to the eventual death of the bone tissue, which results in significant morbidity and reduced quality of life. Diagnostic imaging tests would have moderate impact on morbidity and quality of life in the adult population and significant impact in the pediatric population.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	**Adult osteomyelitis** No specific information was found regarding the relative impact on acceptability to adults of ^{18}FDG-PET, or leukocyte scan. All of these alternatives are likely to be well tolerated, although patients may have some concern over the radiation exposure associated with each alternative. *Bone scintigraphy:* Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. *CT:* Patients may have concerns about radiation exposure and potential side effects of contrast agents. Patients may also feel claustrophobic while in the scanner. *MRI:* Patients undergoing MRI are susceptible to anxiety, panic, or claustrophobia during and after the test.[30,31] Patients also have problems accepting the injection of the contrast dye (e.g., nausea, vertigo, metallic taste), holding their breath, and remaining still on the MRI table, and may not be confident in the diagnostic procedure itself.[31-34] *^{18}FDG-PET* Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. Patients undergoing ^{18}FDG-PET are required to fast prior to the scan.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>Pediatric osteomyelitis

In addition to the concerns listed above, children undergoing CT or MRI may require sedation to ensure they remain still for the duration of the examination.[35-37]

U/S: In children, U/S is often preferred to other imaging tests, as there is no radiation and the test does not require sedation of children.[13]

Overall, bone scanning with ^{99m}Tc-radiolabelled isotopes is:
• minimally more acceptable than CT scanning in both adult and pediatric patients
• minimally less acceptable than ^{18}FDG-PET in adult patients
• minimally less acceptable than MRI in adult patients
• moderately more acceptable than MRI in pediatric patients
• similarly acceptable to leukocyte scanning in adult patients
• minimally less acceptable than U/S in pediatric patients.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>Adult acute osteomyelitis

The review of the current literature yielded two meta-analyses (MAs), one systematic review (SR), and two primary studies that evaluated various comparators in the diagnosis of osteomyelitis, including bone scintigraphy.[24-27,38] The results of studies that evaluated various comparators in the diagnosis of osteomyelitis including bone scintigraphy are summarized in the table:
<table>
<tr><th>Test</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><th colspan="3">MAs (Pooled Data Results)[24,25]</th></tr>
<tr><td>Bone scan</td><td>81 to 90.3</td><td>28.0 to 84.5</td></tr>
<tr><td>Bone biopsy</td><td>Reference Standard</td><td>Reference Standard</td></tr>
<tr><td>MRI*</td><td>88.2 to 90.1</td><td>73.9 to 98</td></tr>
<tr><td>^{18}FDG-PET</td><td>94.1</td><td>87.3</td></tr>
<tr><td>Leukocyte scan</td><td>74 to 89</td><td>68 to 83.8</td></tr>
<tr><th colspan="3">SRs[26]</th></tr>
<tr><td>Bone scan</td><td>78 to 84</td><td>33 to 50</td></tr>
<tr><td>^{18}FDG-PET</td><td>28.6 to 100</td><td>70 to 90</td></tr>
</table></td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		Primary Study[27]
		Bone scan: 86 / 100
		CT: 50 / 85
		^{18}FDG-PET: 43 / 67

CT = computed tomography; ^{18}FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; MA = meta-analysis; MRI = magnetic resonance imaging; SR = systematic review.

*NB: Kapoor et al.[25] reported a range of 77.3% to 100% and 44% to 100% for the sensitivity and specificity of MRI, respectively, However, only pooled sensitivities and specificities were included in this table.

Pediatric acute osteomyelitis

Bone scintigraphy has been demonstrated to be the best predictor of osteomyelitis and MRI results are secondary to it.[19] CT would be the next preferred test, with U/S yielding the lowest diagnostic odds ratio (DOR).

Test	Sensitivity (%)	Specificity (%)
Bone scan	81	84
U/S	55	47
MRI	81	67
CT	67	50

CT = computed tomography; MRI = magnetic resonance imaging; U/S = ultrasound.

Overall, the diagnostic accuracy of bone scanning using ^{99m}Tc-radiolabelled isotopes is:

- moderately better than that of CT in both adult and pediatric patients
- minimally better than that of ^{18}FDG-PET in adult patients
- minimally lower than that of leukocyte scanning in adult patients
- similar to that of MRI in adult patients
- minimally better than that of MRI in pediatric patients
- significantly better than that of U/S in pediatric patients.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
8	**Relative risks associated with the test**	**Non–radiation-related Risks** Bone scanning has been reported to be safe to use and few allergic reactions have been described.[39,40] The overall rate of adverse reactions to radiopharmaceuticals is reported to be between 1 and 2 per 100,000 doses.[40] With CT and MRI, some patients may experience an allergic reaction or side effect from the contrast agent. The frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%) and the frequency of moderate reactions ranges from 0.004% to 0.7%.[41] **Radiation-related Risks** Among the modalities used to detect osteomyelitis, with the exception of MRI and U/S, all tests expose the patient to ionizing radiation. In general, gallium scan, ^{18}FDG-PET, and leukocyte scan confer larger doses of radiation than bone scanning. Overall, bone scanning using ^{99m}Tc-radiolabelled isotopes: • has a similar safety profile to that of CT in both adult and pediatric patients • is minimally safer than ^{18}FDG-PET in adult patients • is minimally safer than leukocyte scanning in adult patients • is minimally less safe than MRI in adult patients • is minimally safer than MRI in pediatric patients • is minimally less safe than U/S in pediatric patients.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
9	**Relative availability of personnel with expertise and experience required for the test**	As of 2006 in Canada, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, 1,781 nuclear medicine technologists, and 2,900 sonographers available across Canada. The Territories do not have the available personnel to perform and interpret tests for osteomyelitis. Other jurisdictions (e.g., Prince Edward Island) may offer limited nuclear medicine services. Assuming the equipment is available, if bone scanning using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that: • more than 95% of procedures could be performed in a timely manner using CT in both adult and pediatric patients • fewer than 25% of the procedures can be performed in a timely manner using ^{18}FDG-PET in adult patients • 75% to 94% of the procedures can be performed in a timely manner using leukocyte scanning in adult patients • 75% to 94% of the procedures can be performed in a timely manner using MRI in both adult and pediatric patients • 25% to 74% of the procedures can be performed in a timely manner using U/S in pediatric patients.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
10	**Accessibility of alternative tests (equipment and wait times)**	No nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[42] The average wait time for urgent bone scan in 2010 ranged from 1 to 6 days, and for non-urgent scans, ranged from 7 to 73 days.[43] No CT scanners are available in Nunavut,[42] and no MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[42] The median CT and MRI wait times ranged from 8 to 22 days and 30 to 75 days, respectively.[43] Another report stated that the mean wait time for CT was 4.6 weeks and MRI was 8.9 weeks.[44] As of November 2010, there were approximately 31 Canadian centres performing publicly funded PET scans.[45] These centres are all located in British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[45] U/S machines are considered to be widely available. Assuming the personnel is available, if bone scanning using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that: • more than 95% of procedures could be performed in a timely manner using CT in both adult and pediatric patients • fewer than 25% of the procedures can be performed in a timely manner using ^{18}FDG-PET in adult patients • 75% to 94% of the procedures can be performed in a timely manner using leukocyte scanning in adult patients • 25% to 74% of the procedures can be performed in a timely manner using MRI in both adult and pediatric patients • more than 95% of the procedures can be performed in a timely manner using U/S in pediatric patients.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of bone and gallium scan with ^{99m}Tc-based radioisotopes is $471.50. ^{18}FDG-PET is significantly more costly than bone scintigraphy. Leukocyte scintigraphy and MRI are minimally more costly than bone scintigraphy. CT is minimally less costly. U/S is moderately less costly.

<table>
<tr><th colspan="3">Relative Costs</th></tr>
<tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr>
<tr><td>Bone and gallium scan</td><td>471.50</td><td>Reference</td></tr>
<tr><td>CT</td><td>262.56</td><td>–208.94</td></tr>
<tr><td>Leukocyte scan</td><td>586.01</td><td>+114.51</td></tr>
<tr><td>MRI</td><td>577.00</td><td>+105.50</td></tr>
<tr><td>^{18}FDG-PET</td><td>1050.00</td><td>+578.50</td></tr>
<tr><td>U/S</td><td>49.15</td><td>–422.35</td></tr>
</table>
</td></tr>
</table>

CT = computed tomography; DOR = diagnostic odds ratio; ^{18}FDG-PET = ^{18}F-fluorodeoxyglucose positron emission tomography; Gd = gadolinium; MRI = magnetic resonance imaging; SCD = sickle-cell disease; ^{99m}Tc-MDP = technetium-99 methylene diphosphonate; U/S = ultrasound.

CRITERION 1: Size of affected population (link to definition)

Adult acute osteomyelitis

In 1972, Lidgren and Lindberg estimated that acute osteomyelitis affects 10 in 100,000 people in the developed world each year.[1] Common sites of infection include the pelvis, sacroiliac joints, hip joints, and femur. Osteomyelitis is more common in males than in females (approximately two-thirds of all cases are male);[1] however, the reasons for this are unknown.[1,5] Joint replacement surgery is recognized as a primary cause of adult acute osteomyelitis.[2] Tsakonas and colleagues reported that of the 58,351 patients who underwent hip and knee surgery in Canada in 2005-2006, 780 (1.3%) had a joint infection within one year of surgery.[14]

Pediatric osteomyelitis

Osteomyelitis occurs in infants and in children between eight and 14 years of age.[1] The Alberta's Children's Hospital reported that 16 cases per 10,000 admissions were diagnosed with osteomyelitis in 2005.[2] The male to female ratio was 1.9 to 1, demonstrating again that boys were almost twice as likely to have the disease. The majority of cases (83%) were diagnosed as acute osteomyelitis.[12] In neonates, osteomyelitis is more frequent, occurring in one in 1,000 neonates.[2]

Subpopulations of osteomyelitis

SCD
A Cochrane Review on the use of antibiotics to treat osteomyelitis in people with SCD noted that osteomyelitis is one of the most common infectious complications in people with SCD.[46] The prevalence of osteomyelitis among people with SCD is estimated to be in the range of 12% to 17.8%.[46] Currently, it is estimated that 8,605 Canadians have SCD,[47] roughly equating to 1,033 to 1,500 cases of osteomyelitis.

Diabetes
According to the Canadian Diabetes Association, more than 9 million Canadians are living with diabetes or prediabetes.[48] According to a previous CADTH report, the annual rate of diabetic foot infection is estimated at 36.5 per 1,000 patients with diabetes in settings with good access to health care, and approximately 15% of patients with diabetes will develop foot osteomyelitis during the course of their disease.[12]

HIV/AIDS
Osteomyelitis is the second most common cause of infection in patients with HIV or AIDS and is most commonly found in the hip. As of 2009, there were more than 69,000 adult Canadians with HIV or AIDS.[49] HIV patients are also susceptible to a unique form of osteomyelitis called "bacillary angiomatoid osteomyelitis," caused by rickettsia-like bacteria.[1]

Athletes
The presence of groin pain in athletes ranges from 5% to 13%.[9] Groin pain can be a symptom of osteomyelitis of the pubis. Although the exact etiology of this disease in this subpopulation is unknown, it is thought that trauma experienced to the symphysis pubis during sports-related activity may make it susceptible to bacterial infection. Osteomyelitis of the pubis appears to be a male-dominated disease.[9]

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Timeliness

Timing of diagnosis in acute osteomyelitis is crucial, as osteomyelitis is a progressive disease. Failure to diagnose and treat promptly can lead to progressive infection, resulting in inflammatory destruction, necrosis, and bone deformation, which can progress to a chronic and persistent stage.[4] Early intervention (within 10 to 20 days of infection)[2] can lead to accurate treatment with an antibiotic regimen,[8,14,26] prevention of chronic osteomyelitis,[7,14] and long-term morbidity in 60% of cases.[7] In osteomyelitis of the diabetic foot, for example, the infection can be restricted to a certain area in the bone and allow for wound healing if the infection is detected early in the disease development.[7]

Urgency

According to the urgency classifications developed by the Saskatchewan Ministry of Health, the urgency of bone, white blood cell (WBC or leukocyte), or gallium scan for the evaluation of suspected osteomyelitis is two to seven days (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). MRI for chronic osteomyelitis is also recommended within two to seven days from the time and date on which the request for an examination is received by the imaging department to the date on which the examination is performed.[50] X-rays of early-phase acute osteomyelitis often appear normal.[2] According to Pineda et al., osteomyelitis must compromise 30% to 50% of bone mineral content and be a minimum of 1 cm in order to be noticeable in plain radiographs.[13]

Pediatric acute osteomyelitis

In children, early findings and subtle changes are not visible on x-ray images until five to seven days after onset of disease,[13] or until two weeks after onset of infection.[17] Bone scans can identify these features within 24 to 49 hours of the onset of infection.[17] Pediatric osteomyelitis is often found in the long bones, and a delay in diagnosis can lead to damage of the growing cartilage and arrest of bone lengthening.[17]

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Osteomyelitis can lead to septicemia[28] and, in rare cases, death.[29] Statistics Canada data demonstrate that in 2007, 83 patients died from osteomyelitis (ICD-10 code M86).[51] None of the deaths were coded as acute cases.[51] It is not known whether any of these deaths could have been avoided with more timely diagnostic imaging.

Mortality rates among diabetics[52,53] and HIV patients[1] have been reported.

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

A prompt diagnosis of acute osteomyelitis can prevent further complications, including sepsis, fractures of the infected bone, deforming bone damage, and soft tissue damage.[13,14,17,54,55] Failure to perform a diagnostic imaging test can therefore have a negative impact on patient morbidity and quality of life.
In a population with diabetic foot, the risk of amputation is 5% to 42%.[7,8,52] A study by Eckman et al. conducted a quality of life survey in patients with non–insulin-dependent diabetes mellitus (NIDDM) who experienced an amputation.[10] The 36-item Short Form health status questionnaire (SF-36) is a self-administered survey that allows patients to rate their general health status on different health attributes, yielding a score of 0 (poorest health) to 100 (best health).[56] Diabetic patients who underwent amputation rated their overall health a score of 49.1, compared with 69.1 for diabetic patients who had not undergone amputation.[10]

In the pediatric population, failure to treat osteomyelitis can have serious long-term consequences, including chronic bone damage, limb deformity, and sepsis.[57] Brodie abscess — a type of subacute osteomyelitis — is common in children, especially boys, and is usually found in the distal and proximal portions of the tibia.[13]

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CRITERION 5: Relative impact on health disparities (link to definition)

Osteomyelitis affects people with underlying health problems, such as SCD, diabetes, or AIDS, more frequently than it does healthy individuals. Osteomyelitis is more common in males than in females (approximately two-thirds of all cases are male).[1] For example, a recent systematic review found that only nine (5.3%) of 171 athletes with osteomyelitis or osteitis pubis were female.[9]

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

The following are applicable to adults or children with suspected osteomyelitis:

Bone scanning
Limited information was identified on the acceptability of bone scanning to patients. A retrospective study on the use of bone scanning in children with osteosarcoma or Ewing sarcoma suggested that any test, including a bone scan, causes psychological strain on the children and the parents.[58] Patients, or parents of patients, may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

CT
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This may be less of a problem with new CT scanners, if available (MIIMAC expert opinion). Patients may also be required to hold their breath for a substantial period of time, which is seen as “uncomfortable” and “difficult.”[59] Children undergoing CT may require sedation. Sedation may be avoided by depriving the child of sleep and feeding him or her prior to the test.[60]

^{18}FDG-PET
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

Leukocyte scan ^{111}In-WBC
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia as well as be bothered by the noise; however, this may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[30,31] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. The entire MRI exam takes 30 to 60 minutes and children and infants are often sedated to ensure that they remain still for the duration of the examination.[60] Sedation may be avoided by depriving the child of sleep and feeding him or her prior to the test.[60]

U/S
Some discomforts associated with U/S include cold, unspecified pain, and tenderness. In a study comparing U/S with MRI in undiagnosed shoulder pain, 100% of the patients participating said that they would be willing to undergo the U/S exam again.[33] This test may be preferred in pediatric patients as there is no exposure to ionizing radiation or radiation, and the test does not require sedation of children.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Four studies[24-27] were identified pertaining to the diagnostic accuracy of imaging in cases of suspected osteomyelitis: two MAs,[24,25] one SR,[26] and two primary studies.[27,38] Review papers that were systematic in their methods were not included. Three studies evaluated the diagnostic accuracy of radiographs (x-ray),[24,25,27] two evaluated leukocyte scan,[24,26] three evaluated MRI,[24,25,27] three ^{18}FDG-PET,[24,26,38] and two CT.[24,27] No studies assessed the diagnostic accuracy of U/S for osteomyelitis. A high-level summary of the included studies is included below and further detail is provided in Appendix 3.

Meta-analyses

Dinh et al. [24]
This MA evaluated the diagnostic accuracy of imaging tests for diagnosis of osteomyelitis in diabetic patients with foot ulcers.[24] A histopathological examination or microbial culture of bone specimens was the gold standard required for study inclusion.[24] A total of 917 articles were found in the literature search (1966 to February 27, 2007), nine of which were included in the analysis.[24] An additional 59 studies were identified by searching reference lists of potentially relevant articles.[24] Although the search strategy included six imaging comparators (MRI, CT, bone scan, PET, leukocyte scan, and x-ray), the authors were unable to find a study evaluating either CT or PET that met their inclusion criteria.[24] Pooled sensitivity and specificity, the summary measure of accuracy (Q*), and diagnostic odds ratio (DOR) were calculated.[24]

Six of the nine studies included bone scintigraphy as a comparator. The final pooled sensitivity and specificity were 0.81 (95% CI, 0.73 to 0.87; P < 0.001) and 0.28 (95% CI, 0.17 to 0.42; P = 0.01), respectively. The DOR was 2.10, indicating poor discriminating ability compared with biopsy. The Q* value was 0.62, suggesting moderate accuracy for diagnosis of osteomyelitis.[24]

Four studies of plain radiography (x-rays) met the inclusion criteria. Pooled sensitivity and specificity for diagnosis of osteomyelitis was 0.54 (95% CI, 0.44 to 0.63; P = 0.006) and 0.68 (95% CI, 0.53 to 0.80; P = 0.01), respectively. The DOR was 2.84 and the Q* score 0.60, indicating low-to-moderate accuracy.[24]

Six of the nine studies evaluated ^{111}In-leukocyte scan as a comparator and the final pooled sensitivity and specificity were 74.0 and 68.0, respectively, while the DOR was 2.84. The Q* value was 0.60, indicating low-to-moderate accuracy.[24]

Four studies evaluated the use of MRI. Pooled sensitivity and specificity was 0.90 (95% CI, 0.82 to 0.95) and 0.79 (95%CI, 0.62 to 0.91). The DOR was 24.36, indicating excellent discriminatory power of MRI. The Q* score was 0.74, highest amongst included diagnostic tests.[24]

Kapoor et al.[25]
This MA evaluated the diagnostic accuracy of MRI for osteomyelitis of the foot and compared this with bone scanning, plain radiography, and WBC studies.[25] A total of 2,070 articles were found from the literature search (1966 to June 2006), 16 of which were included in the analysis.[25] Eleven of the 16 studies included almost exclusively diabetic patients.[25] Seven studies compared MRI with ^{99m}Tc bone scanning, nine with plain radiography, and three with WBC scanning.[25] Results demonstrated that the DOR for MRI was consistently better than for bone scanning (seven studies — 149.9 [95% CI, 54.6 to 411.3] for MRI versus 3.6 [95% CI, 1.0 to 13.3]) for bone scan, x-ray (nine studies — 81.5 [95% CI, 14.2 to 466.1] for MRI versus 3.3 [95% CI, 2.2 to 5.0) for x-ray), and WBC studies (three studies — 120.3 [95% CI, 61.8 to 234.3] versus 3.4 [95% CI, 0.2 to 62.2]). Hence, MRI was a stronger predictor of osteomyelitis in the foot and ankle than either ^{99m}Tc bone scan or x-ray.[25]

Systematic review

Van der Bruggen et al.[26]
A recent SR by Van der Bruggen and colleagues assessed the diagnostic accuracy of different imaging tests including scintigraphy and ^{18}FDG-PET, for imaging of osteomyelitis and prosthetic bone and joint infections.[26] The authors conclude that because of considerable heterogeneity between studies, pooled sensitivity and specificity calculations are not possible.[26] Of the 29 articles (N = 1,054 patients) of ^{18}FDG-PET identified, the authors conclude that this imaging technique is adequate for chronic (note: not acute) osteomyelitis.[26]

Primary studies

Larson et al.[27]
Larson and colleagues recently performed a retrospective chart review of patients with pressure ulcer in the United States to access the diagnostic accuracy of preoperative x-ray or CT scan (obtained up to one year preoperatively) compared with results of bone biopsy taken during surgical debridement.[27] Charts of 44 patients indicated that 50% of patients with biopsy-proven osteomyelitis were identified by preoperative CT scans, compared with 88% using x-ray. Interestingly, 85% of patients without biopsy-proven osteomyelitis were detected by

preoperative CT scan and 32% with x-ray. The overall sensitivity of either radiologic study was 61% and the overall specificity of both studies was 69%.[27]

Familiari et al.[38]
Familiari and colleagues recently conducted a prospective observational study in Europe to compare the diagnostic accuracy of ^{99m}Tc exametazime WBC scintigraphy and sequential ^{18}F-FDG-PET/CT for diagnosis of osteomyelitis in the diabetic foot. Thirteen diabetic patients (12 male and one female; mean age 62.2 ± 10.9 years) with suspected osteomyelitis were enrolled. After bone biopsy (gold standard), osteomyelitis was confirmed in seven patients, two patients had soft-tissue infection without bone involvement, and four patients had no infection. ^{99m}Tc exametazime WBC scintigraphy was found to have a sensitivity of 86% and specificity of 100%; the positive and negative predictive values were 100% and 86%, respectively. Conversely, ^{18}FDG-PET/CT had a sensitivity of 43% and specificity of 67%; the positive and negative predictive values were 60% and 50%, respectively. The authors conclude that ^{18}FDG PET/CT has a low diagnostic accuracy for osteomyelitis and cannot replace ^{99m}Tc exametazime WBC scintigraphy in patients with diabetic foot.[38]

Pediatric acute osteomyelitis

No MAs, SRs, or review papers with information regarding the diagnostic accuracy, specific to a pediatric population, were found. One primary study[19] was found that specifically evaluated the accuracy of imaging modalities in the diagnosis of acute osteomyelitis in a pediatric population.

Malcius et al.[19]
A study conducted in Lithuania by Malcius and colleagues examined the accuracy of several radiological tests in the diagnosis of osteomyelitis, specifically in a pediatric population.[19] Children aged one to 18 years were eligible for participation and a total of 183 patients (mean age of 10.3 years) were enrolled.[19] The following tests were performed: bone scan (^{99m}Tc), x-ray, MRI, CT, and U/S.[19] For a complete summary of diagnostic accuracy of tests, refer to Appendix 3.[19] The authors concluded that late x-ray (taken a median of 15 days after hospitalization) is the most accurate imaging method, followed by bone scan and MRI (at the onset of disease).[19]

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Bone scanning
Several studies[61-64] reported mild adverse events with ^{99m}Tc-labelled tracers (e.g., skin reactions), and one case report published in 1985 reported a patient who experienced a rash following two bone scans with ^{99m}Tc-MDP, one in 1983 and one the following year.[65] The authors concluded this patient had an allergic reaction to MDP on both occasions. This case report references an older study that reported 22 adverse reactions to ^{99m}Tc-MDP, in which 20 of the reactions were either “probably” or “possibly” caused by MDP.

CT
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[66] In addition, patients may experience mild side effects from the contrast agent, such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium (Gd) contrast materials

administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[67] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. According to the American College of Radiology *Manual on Contrast Media*,[41] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[41]

^{18}FDG-PET
The Pharmacopeia Committee of the Society of Nuclear Medicine (SNM) conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[68]

Leukocyte scan
Several studies[61,64,69] reported mild adverse events with ^{99m}Tc-labelled tracers, including those used to label WBC (e.g., skin reactions). No reaction rates were provided.

MRI
MRI is contraindicated in patients with metallic implants, including pacemakers.[70] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[66] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media,*[41] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[41]

U/S
There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

Among the modalities available to diagnose acute osteomyelitis, bone scan, leukocyte scan, gallium scan, PET, and CT expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 2. Radiation exposure can be a concern for testing pediatric patients, as the risk of radiation-induced cancer is two to three times greater in children and adolescents than in adult patients.[71]

Table 2 : Effective Doses of Radiation		
Procedure	**Average Effective Dose (mSv)**	**Pediatric Effective Dose (mSv)**
^{99m}Tc-labelled tracers bone scan[28,72]	1 to 10	0.03 to 3
CT[28,72,73]	Less than 0.1 to 7.3	Less than 0.03
^{18}FDG-PET[72]	10 to 30	3 to 10
Leukocyte scan[28]	10.0	NA
MRI[72]	0	0
U/S[72]	0	0
Average background dose of radiation per year	1 to 3.0[74-76]	1 to 3.0[74-76]

CT = computed tomography; ^{18}FDG-PET = ^{18}F-fluorodeoxyglucose Positron Emission Tomography; MRI = magnetic resonance imaging; mSv = millisievert; NA = not available; ^{99m}Tc = technetium-99m; U/S = ultrasound.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required to perform imaging tests to diagnose osteomyelitis are presented by imaging modality. A summary of the availability of personnel required for the conduct of methods to diagnose osteomyelitis by bone scintigraphy or any of the alternative imaging modalities is provided in Table 3.

Bone scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of bone scans should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[77] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct bone scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body. Expertise in pediatric imaging may be required.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and U/S should be diagnostic radiologists[78] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[77] Expertise in pediatric imaging may be required.

Medical radiation technologists (MRTs) must be certified by CAMRT or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification

will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on-site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, magnetic resonance (MR) scanners, and nuclear medicine equipment.[77]

CT
For the performance of CT scan, MRTs who are certified by CAMRT or an equivalent licensing body recognized by CAMRT are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

^{18}FDG-PET
In Canada, physicians involved in the performance, supervision, and interpretation of PET scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Technologists must be certified by CAMRT or an equivalent licensing body.

Leukocyte scan
Leukocyte scanning requires the same personnel as bone scanning with ^{99m}Tc-based radioisotopes. No literature was identified regarding the expertise required for handling and processing WBCs.

MRI
For the performance of MRI, medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

U/S
Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification from the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[78] In Quebec, sonographers and MRTs are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[78]

Table 3: Medical Imaging Professionals in Canada[78]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	Medical Radiation Technologists	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR

Table 3: Medical Imaging Professionals in Canada[78]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**Medical Radiation Technologists**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PEI = Prince Edward Island; QC = Quebec; YT = Yukon.
*This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 4 provides an overview of the availability of equipment required to diagnose osteomyelitis. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010. Data were not available for U/S.

Table 4: Diagnostic Imaging Equipment in Canada[42,45,78]					
	Nuclear Medicine Cameras	**CT Scanners**	**MRI Scanners**	**SPECT/CT Scanners**	**PET or PET/CT**
Number of devices	603[78]	460[42]	218[42]	96[42]	36[45]
Average number of hours of operation per week (2006-2007)[78]	40	60	71	NR	NR
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	PEI, YT, NT, NU	NL, PEI, SK, YT, NT, NU

CT = computed tomography; MRI = magnetic resonance imaging; NL = Newfoundland and Labrador; NR = not reported; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; PET = positron emission tomography; PET/CT = positron emission tomography/computed tomography; SK = Saskatchewan; SPECT/CT = single-photon emission computed tomography/computed tomography; YT = Yukon.

Bone scanning

For bone scintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[78]

CT

No CT scanners are available in Nunavut.[78] The average weekly use of CT scanners ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[78] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[44]

^{18}FDG-PET

A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[45] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[45] There are 36 PET or PET/CT scanners, four of which are used for research purposes only.[45]

Leukocyte scan

It was assumed that leukocyte scan was considered a nuclear imaging test and therefore the wait for bone tests was, on average at one Montreal hospital, eight days.[79] Data from 2007 state that nuclear imaging cameras are available at a rate of 18.4 per million people. However, there are no cameras available in the Yukon Territories, Northwest Territories, or Nunavut.[44]

MRI

No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[78] According to the Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006-2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario, with a national average of 71 hours.[78] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[44]

U/S

U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[44]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of bone scanning and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical or surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 5), the cost of bone and gallium scan with ^{99m}Tc-based radioisotopes is $471.50. CT is a minimally less costly alternative and ^{18}FDG-PET is significantly more costly than bone scintigraphy, and leukocyte scintigraphy and MRI are both minimally more costly than bone scintigraphy. U/S is moderately less costly.

Table 5: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[80]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
Bone and Gallium Scintigraphy				
J867	Blood flow and pool imaging	58.75	29.30	88.05
J851	Bone scintigraphy — single site	87.00	50.95	137.95
J853	Gallium scintigraphy — single site	126.85	50.95	177.80
Maintenance fees — global budget		67.70		67.70
	TOTAL	340.30	131.20	**471.50**
CT				
X231	CT — pelvis — without IV contrast		91.15	91.15
Technical cost — from global budget		150.00		150.00
Maintenance fees — from global budget		21.41		21.41
	TOTAL	171.41	91.15	**262.56**
Leukocyte Scintigraphy				
J884B and J884C	^{111}In leukocyte scintigraphy — single site	329.00	50.95	379.95
J866B and J866C	Application of tomography (SPECT), maximum 1 per nuclear medicine examination	44.60	31.10	75.70
J867B and J867C	First transit — with blood pool images	58.75	29.30	88.05
Maintenance fees — from global budget		42.31		42.31
	TOTAL	474.66	111.35	**586.01**
MRI				
X471	Multislice sequence, 1 extremity and/or 1 joint		66.10	66.10
X475C x3	Repeat (another plane, different pulse sequence; to a maximum of 3 repeats)		99.30	99.30
X487	When Gd is used		38.60	38.60
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	373.00	204.00	**577.00**
^{18}FDG-PET				
Proxy code	Professional fee for PET		250.00	250.00
Technical cost — from global budget		800.00		800.00
	TOTAL	800.00	250.00	**1050.00**
U/S				
J182	Extremities — per limb	26.15	19.70	45.83
Maintenance fees — global budget		3.30		3.30
	TOTAL	29.45	19.70	**49.15**

CT = computed tomography; ^{18}FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; Gd = gadolinium; ^{111}In = Indium 111; IV = intravenous; MRI = magnetic resonance imaging; PET = positron emission tomography; prof. = professional; SPECT = single-photon emission computed tomography; tech. = technical; U/S = ultrasound.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test who are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1948 to February 18, 2011>
Date of Search:	February 22, 2011
Alerts:	Monthly search updates began February 22, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	No date limit for systematic reviews; publication years 2006 – February 2011 for primary studies English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Ovid MEDLINE Strategy	
Line #	**Search Strategy**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	radioisotope*.mp.
6	(technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc*

Ovid MEDLINE Strategy	
	or 99mtechnetium* or 99m-technetium*).tw,nm.
7	Radionuclide Imaging/
8	Bone Diseases, Infectious/ri
9	Osteomyelitis/ri
10	(((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)) or scintigraph* or scintigram* or scintiphotograph*).tw.
11	(bone* adj5 (imaging or scan*)).tw.
12	(WBC adj5 (imaging or scan*)).tw.
13	(white blood cell* adj5 (imaging or scan*)).tw.
14	(leukocyte* adj5 (imaging or scan*)).tw.
15	or/1-14
16	Osteomyelitis/
17	Bone Diseases, Infectious/
18	(osteomyelitis or osteomyelitides).tw.
19	(bone* adj inflammation*).tw.
20	(bone* adj3 infection*).tw.
21	or/16-20
22	Meta-Analysis.pt.
23	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
24	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
25	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
26	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
27	(data synthes* or data extraction* or data abstraction*).tw.
28	(handsearch* or hand search*).tw.
29	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.
30	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).tw.
31	(meta regression* or metaregression* or mega regression*).tw.
32	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
33	(medline or Cochrane or pubmed or medlars).tw,hw.
34	(cochrane or health technology assessment or evidence report).jw.
35	or/22-34
36	exp "Sensitivity and Specificity"/

Ovid MEDLINE Strategy	
37	False Positive Reactions/
38	False Negative Reactions/
39	du.fs.
40	sensitivit*.tw.
41	(predictive adj4 value*).tw.
42	distinguish*.tw.
43	differentiat*.tw.
44	enhancement.tw.
45	identif*.tw.
46	detect*.tw.
47	diagnos*.tw.
48	accura*.tw.
49	comparison*.tw.
50	Comparative Study.pt.
51	(Validation Studies or Evaluation Studies).pt.
52	Randomized Controlled Trial.pt.
53	Controlled Clinical Trial.pt.
54	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
55	Multicenter Study.pt.
56	(random* or sham or placebo*).ti.
57	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
58	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
59	(control* adj3 (study or studies or trial*)).ti.
60	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
61	(allocated adj "to").ti.
62	Cohort Studies/
63	Longitudinal Studies/
64	Prospective Studies/
65	Follow-Up Studies/
66	Retrospective Studies/
67	Case-Control Studies/
68	Cross-Sectional Study/
69	(observational adj3 (study or studies or design or analysis or analyses)).ti.
70	cohort.ti.
71	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.

Ovid MEDLINE Strategy	
72	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
73	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
74	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
75	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
76	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
77	(population adj3 (study or studies or analysis or analyses)).ti.
78	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
79	or/36-78
80	Case Reports.pt.
81	79 not 80
82	15 and 21 and 35
83	limit 82 to english language
84	15 and 21 and 81
85	limit 84 to (english language and humans and yr="2006 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 1, 2011	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 2011
Keywords:	Included terms for radionuclide imaging and osteomyelitis.
Limits:	No limits

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters), were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Diagnostic Accuracy

Table 6: Diagnostic Accuracy of Bone Scan and the Alternative Tests Based on the Information Presented in the Included Studies

Test	Author	Reference Standard	Outcome						
			Sens %	Spec %	Acc %	DOR	PPV %	NPV %	Localization Rate
Bone scan	Dinh et al. 2008	Bone Biopsy/Surgery	81.0	28.0	NR	2.10	NR	NR	NR
	Kapoor et al. 2007	Bone Biopsy/Surgery (head-to-head studies)	90	28.5	-	3.6	NR	NR	NR
	Eckman et al. 1996	Bone Biopsy/Surgery	86	45	NR	NR	NR	NR	NR
	Van der Bruggen et al. 2010*	Bone Biopsy/Surgery	78 to 84	33 to 50	NR	NR	NR	NR	NR
	Familiari et al. 2011	Bone Biopsy (diabetic population)	86	100	92	NR	100	86	NR
X-ray	Dinh et al. 2008	Bone Biopsy/Surgery	54.0	68.0	NR	2.84	NR	NR	NR
	Eckman et al. 1996	Bone Biopsy/Surgery	62.0	64.0	NR	NR	NR	NR	NR
	Larson et al. 2010†	Bone Biopsy/Surgery	88.0	32.0	NR	NR	NR	NR	NR

Table 6: Diagnostic Accuracy of Bone Scan and the Alternative Tests Based on the Information Presented in the Included Studies

Test	Author	Reference Standard	Outcome						
			Sens %	Spec %	Acc %	DOR	PPV %	NPV %	Localization Rate
MRI	Kapoor et al. 2007	Bone Biopsy/Surgery (head-to-head studies)	90	98	NR	149.9	NR	NR	NR
		Bone Biopsy/Surgery	77.3 to 100	44 to 100	NR	42.1	NR	NR	NR
	Dinh et al. 2008	Bone Biopsy/Surgery	90.0	79.0	NR	24.36	NR	NR	NR
^{18}FDG-PET/PET-CT	Van der Bruggen et al. 2010*	Bone Scan	78	70	74	NR	NR	NR	NR
		Bone Biopsy/Surgery	94 to 100	87 to 100	NR	NR	NR	NR	NR
		Bone Biopsy/Surgery (diabetic population)	28.6 to 100	NR	NR	NR	NR	NR	NR
		Bone Biopsy/Surgery (orthopediatric implant infection)	< 30	90	NR	NR	NR	NR	NR
	Familiari et al. 2011	Bone Biopsy (diabetic population)	43	67	54	NR	60	50	NR
CT	Larson et al. 2010†	Bone Biopsy/Surgery	50	85	NR	NR	NR	NR	NR

Table 6: Diagnostic Accuracy of Bone Scan and the Alternative Tests Based on the Information Presented in the Included Studies

Test	Author	Reference Standard	Outcome						
			Sens %	Spec %	Acc %	DOR	PPV %	NPV %	Localization Rate
Leukocyte scan	Dinh et al. 2008	Bone Biopsy/Surgery	74	68	NR	10.07	NR	NR	NR
	Eckman et al. 1996	Bone Biopsy/Surgery	89.0	79.0	NR	NR	NR	NR	NR
	Van der Bruggen et al. 2010*	Bone Biopsy/Surgery	NR	NR	NR	NR	NR	NR	47%

Acc = accuracy; bone scan = bone scintigraphy; CT = computed tomography; DOR = diagnostic odds ratio; MRI = magnetic resonance imaging; NLR = negative likelihood ratio; NPV = negative predictive value; NR = not reported; PLR = positive likelihood ratio; PPV = positive predictive value, sens= sensitivity; spec= specificity.
*Systematic Review
†Primary Study data

Table 7: Summary of Diagnostic Accuracy Measures of the Tests in Pediatric Acute Osteomyelitis[19]								
Test	**Sens %**	**Spec %**	**Acc %**	**PPV %**	**NPV %**	**PLR**	**NLR**	**DOR**
Bone scan	81	84	82	94	59	5.11	0.23	22.3
Bone biopsy/labs	1.0	1.0	NA	NA	NA	NA	NA	NA
CT	67	50	65	91	17	1.33	0.67	2.0
^{18}FDG-PET or PET/CT	NA	NA	NA	NA	NA	NA	NA	NA
U/S	55	47	54	082	19	1.04	0.96	1.08
MRI	81	67	79	93	40	2.44	0.28	8.67
X-ray — early (late)	16	96	27	96	16	3.81	0.88 (0.19)	4.34 (51.17)
Leukocyte scan	NA	NA	NA	NA	NA	NA	NA	NA

Acc = accuracy; bone scan = bone scintigraphy, CT = computed tomography; DOR = diagnostic odds ratio; ^{18}FDG-PET = 18-fluorodeoxyglucose positron emission tomography; MRI = magnetic resonance imaging; NA = not available; NLR= negative likelihood ratio; NPV = negative predictive value; PLR = positive likelihood ratio; PPV = positive predictive value; sens = sensitivity; spec = specificity.

Appendix 4: Definitions

Brodie abscess: A necrotic cavity surrounded by dense granulation tissue.[81] A sequela of chronic bone infection.

Cephalhematomas: A blood cyst, or swelling of the scalp in a newborn due to an effusion of blood beneath the skull, often resulting from birth trauma.[82]

Dead space: A cavity that remains after the incomplete closure of a surgical or traumatic wound, leaving an area in which blood can collect and delay healing.[81]

Dermographism: Inflammation of skin and muscles; generalized itch is frequent with this condition.[83]

Fistulae: An abnormal passage from an internal organ to the body surface or between two internal organs.[81]

ICD-10: International Classification of Diseases (ICD) version 10. The ICD is the international standard diagnostic classification for all general epidemiological, many health management purposes, and clinical use. It is used to classify diseases and other health problems recorded on many types of health and vital records, including death certificates and health records. In addition to enabling the storage and retrieval of diagnostic information for clinical, epidemiological, and quality purposes, these records also provide the basis for the compilation of national mortality and morbidity statistics by World Health Organisation Member States.[84]

Necrosis: Death of areas of tissue or bone surrounded by healthy parts of tissue or bone.[85]

Relative risk (RR): The ratio of the chance of a disease developing among members of a population exposed to a factor, compared with a similar population not exposed to the factor. In many cases, the RR is modified by the duration or intensity of exposure to the causative factors.[86]

Sacroiliac joints: The joint formed by the sacrum and ilium where they meet on either side of the lower back.[81]

Sickle-cell disease (SCD): Or sickle cell anemia (SCA); a severe, chronic, incurable condition that occurs in people homozygous for hemoglobin. The abnormal hemoglobin results in distortion and fragility of the erythrocytes. SCD is characterized by crisis joint pain, thrombosis, and fever, and by chronic anemia with splenomegaly, lethargy, and weakness.[81]

Surgical debridement: The removal of foreign material and devitalized tissue using a scalpel or other sharp instrument.[86]

APPENDIX 2.6

INDICATION OVERVIEW

Radionuclide imaging is used in patients who have new symptoms suggestive of metastasis.[1] Bone scanning is performed in patients with known cancer to detect possible metastasis and is also conducted in patients for staging and subsequent treatment planning.

Population: Patients with cancer (limited to lung, prostate, and breast) undergoing staging and including patients with known cancer presenting with or without bone pain.

Intervention: Bone scanning, also known as bone scintigraphy, using technetium-99m–labelled methylene diphosphonate (^{99m}Tc-MDP).[2]

During a bone scan, the ^{99m}Tc-MDP is injected intravenously and accumulates in bone after several hours.[3,4] A gamma camera is then used to detect "hot spots," which represent the areas of bone that have high metabolism or vasculature where the ^{99m}Tc has accumulated, such as in areas of bone metastasis.

Comparators: For this report, the following diagnostic tests are considered as alternatives to bone scanning:

- *Positron emission tomography (PET) using 18F-fluoride (^{18}F) or 18F-fluorodeoxyglucose (^{18}FDG)*

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 2) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and bone tumours.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. Where possible, retrieval was limited to the human population and English-language documents. No date limits were applied for systematic reviews. For primary studies, the retrieval was limited to documents published between January 1, 2006, and March 14, 2011. Regular alerts were established to update the search until October 2011. See Appendix 2 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google and other Internet search engines were used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

Thirty-one potential articles were identified through the health technology assessment/systematic review/meta-analysis (HTA/SR/MA) filtered search and 12 were subjected to full-text review. A total of 380 potential primary studies were identified with the primary studies search. Additional studies were identified in searches for grey literature, targeted searches, and alerts.

For criterion 7 on diagnostic accuracy, systematic reviews were included. In addition, primary studies published between 2006 and 2011 that were not included in any of the systematic reviews were summarized individually. In total, six systematic reviews[5-10] and five primary studies[11-15] were included for criterion 7.

For all the remaining criteria, included studies were not limited by study design or date, and were obtained from the HTA/SR/MA search, grey literature searching, a primary studies search, targeted searching, and handsearching.

SUMMARY TABLE

<table>
<tr><th colspan="3">Table 1: Summary of Criterion Evidence</th></tr>
<tr><td colspan="3">Domain 1: Criteria Related to the Underlying Health Condition</td></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>1</td><td>Size of the affected population</td><td>The estimated number of new cases of breast, prostate, and lung cancer in 2011 is tabulated. Based on data from a population-based analysis of approximately 100,000 women with breast cancer and 125,000 men with prostate cancer, the incidence of bone metastasis at diagnosis or during follow-up (median 3.3 years) was 7.3%[16] and 7.7%,[17] respectively. Similar data were not available for lung cancer. Studies have reported an incidence of bone metastases of approximately 30% for patients with non–small cell lung cancer.[18] Using these data, the possible number of cases of metastasis was estimated.
<table>
<tr><th colspan="3">Cases of Bone Metastasis</th></tr>
<tr><th>Cancer Type</th><th>2011 Estimated Number of New Cases per 100,000[19]</th><th>Estimated Number of Cases of Bone Metastasis per 100,000*</th></tr>
<tr><td>Breast</td><td>102†</td><td>7.4 (0.0074)</td></tr>
<tr><td>Prostate</td><td>122</td><td>9.5 (0.0095)</td></tr>
<tr><td>Lung</td><td>57</td><td>17.1 (0.0171)</td></tr>
</table>
*Calculated from estimated new cases and the reported rates of bone metastasis for each type of cancer.[20]
†Females only

Notably, these patients would undergo repeat imaging if there is suggestion that there was disease progression to the bone. Therefore, each patient could receive multiple scans. Given this, the size of the affected population is estimated to be more than 1 in 1,000 (0.1%) and less than or equal to 1 in 100 (1%).</td></tr>
<tr><td>2</td><td>Timeliness and urgency of test results in planning patient management</td><td>Imaging to detect bone metastases required for staging to plan treatment and follow-up. Benchmark wait times for bone scan and PET are immediate to 24 hours for an emergency case, within 7 days for an urgent case, and within 30 days for a scheduled case.[21] Patient management (i.e., surgery, chemotherapy, radiation) depends on imaging findings. A delay in test results may have a negative effect on the workflow.

The target time frame for performing the test is between 8 and 30 days, and obtaining the test results has significant impact on the management of the condition or the effective use of health</td></tr>
</table>

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
		care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	The estimated 5-year relative survival ratio (for the period 2004-2006) is 88%, 96%, and 19% for breast, prostate, and lung cancer, respectively. If an imaging test was not performed, staging information cannot be obtained and treatment cannot be appropriately planned. However, if the test was performed, there is ultimately no impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Imaging is required for accurate staging of disease and for selecting the appropriate treatment. Without accurate staging information, patients may receive less aggressive treatment (e.g., a patient with clinical stage I or II disease who would have been restaged to stage III with imaging findings and, subsequently, managed differently) or more aggressive treatment (e.g., surgery being unnecessarily performed on a patient who would not benefit from it, based on diagnostic imaging information — for instance, if they had metastatic disease that has spread throughout the body, which would have been detected by imaging). Diagnostic imaging test results can have a significant impact on morbidity or quality of life.

<table>
<tr><th colspan="3">Table 1: Summary of Criterion Evidence</th></tr>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>5</td><td>Relative impact on health disparities</td><td>To be scored locally.</td></tr>
<tr><td>6</td><td>Relative acceptability of the test to patients</td><td>Bone scanning: Limited information was identified on the acceptability to patients of bone scanning with ^{99m}Tc-MDP. Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

PET: Patients are required to fast prior to an ^{18}FDG-PET scan.

The level of acceptability to patients of bone scanning with ^{99m}Tc-radiolabelled isotopes:
• is similar to ^{18}FDG-PET
• is minimally lower than ^{18}F-PET.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>The sensitivity and specificity of bone scanning, ^{18}FDG-PET, and ^{18}F-PET were reported in 6 systematic reviews and 5 observational studies. For the modality of PET, all of the included studies used the pharmaceutical ^{18}FDG. No primary studies were identified for inclusion (which were not already included in a systematic review) that used ^{18}F. The data are summarized according to cancer type.
<table>
<tr><th colspan="3">Diagnostic Accuracy</th></tr>
<tr><th>Test</th><th>Sensitivity Range (%)</th><th>Specificity Range (%)</th></tr>
<tr><td colspan="3">Detection of Bone Metastases — Breast Cancer</td></tr>
<tr><td>Bone scan</td><td>78 to 100</td><td>80 to 100</td></tr>
<tr><td>^{18}FDG-PET or ^{18}FDG- PET/CT</td><td>78 to 100</td><td>88 to 100</td></tr>
<tr><td colspan="3">Detection of Bone Metastases or Staging — Lung Cancer</td></tr>
<tr><td>Bone scan</td><td>67 to 92</td><td>69 to 94</td></tr>
<tr><td>^{18}FDG-PET or ^{18}FDG- PET/CT</td><td>92 to 96</td><td>97 to 99</td></tr>
<tr><td colspan="3">Detection of Bone Metastases or Staging — Prostate Cancer</td></tr>
<tr><td>Bone scan</td><td>46 to 71</td><td>32 to 100</td></tr>
</table>
CT = computed tomography; ^{18}FDG-PET = 18-fluorodeoxyglucose positron emission tomography.</td></tr>
</table>

<table>
<tr><th colspan="3">Table 1: Summary of Criterion Evidence</th></tr>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>No information was available regarding the diagnostic accuracy of bone scanning and other imaging techniques according to cancer stage.

Overall, with respect to breast cancer, the diagnostic accuracy of bone scanning with ^{99m}Tc-radiolabelled isotopes is:
• similar to ^{18}FDG-PET
• minimally lower than ^{18}F-PET.

Overall, with respect to prostate cancer, based on feedback from MIIMAC, the diagnostic accuracy of bone scanning with ^{99m}Tc-radiolabelled isotopes is:
• moderately lower than ^{18}F-PET.

Overall, with respect to lung cancer, the diagnostic accuracy of bone scanning with ^{99m}Tc-radiolabelled isotopes is:
• moderately lower than ^{18}FDG-PET
• minimally lower than ^{18}F-PET.</td></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>Non–radiation-related Risks
Patients may experience soreness and swelling at the site of injection of the ^{99m}Tc, and there is a small risk of cell or tissue damage due to the radiation. Some patients may have difficulty lying still during the test.[4,22] Although rare, allergic reactions to MDP are possible.[23]

Radiation-related Risks
The radiation dose for bone scans is lower than that of ^{18}FDG-PET/CT.[10] Radiation doses for the modalities used in bone tumour imaging are tabulated.

Effective Doses of Radiation[24,25]
<table><tr><th>Procedure</th><th>Average Dose (mSv)</th></tr><tr><td>Bone scan</td><td>6.3</td></tr><tr><td>Whole body PET</td><td>14.1</td></tr><tr><td>Average backgroud dose of radiation per year</td><td>1 to 3.0[26-28]</td></tr></table>mSv = millisievert; PET = positron emission tomography.</td></tr>
</table>

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		Overall, the safety profile of bone scanning with ^{99m}Tc-radiolabelled isotopes is: • similar to that of ^{18}FDG-PET • similar to that of ^{18}F-PET.
9	**Relative availability of personnel with expertise and experience required for the test**	Interobserver agreement of bone scans has been reported as moderate,[29,30] Another study reported good agreement for bone scanning and ^{18}FDG-PET/CT.[31] As of 2006 in Canada, there were 2,034 diagnostic radiologists; 221 nuclear medicine physicians; 12,255 radiological technologists; 1,781 nuclear medicine technologists, and 2,900 sonographers available across Canada. The Territories do not have the available personnel to perform and interpret tests to detect bone metastases. Other jurisdictions (e.g., PEI) may offer limited nuclear medicine services. Assuming the necessary equipment is available, if bone scanning with ^{99m}Tc radiolabelled isotopes is not available, it is estimated that: • fewer than 25% of the procedures can be performed in a timely manner using ^{18}FDG-PET • fewer than 25% of the procedures can be performed in a timely manner using ^{18}F-PET.
10	**Accessibility of alternative tests (equipment and wait times)**	*Wait times* Wait times for urgent bone scan ranged from 1 to 6 days, and for scheduled scans ranged from 7 to 73 days.[32] *Equipment* Overall, the availability of equipment required for bone scanning is good — except in areas where nuclear medicine services are limited (e.g., Prince Edward Island) or unavailable (all three Territories). As of November 2010, there were approximately 31 Canadian centres performing publicly funded PET scans.[33] These centres are all located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[33] There are 36 PET or PET/CT scanners, 4 of which are used for research purposes only.[33] Assuming personnel with the necessary expertise and experience are available, if bone scanning with ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that: • fewer than 25% of the procedures can be performed in a timely manner using ^{18}FDG-PET • fewer than 25% of the procedures can be performed in a timely manner using ^{18}F-PET.

Table 1: Summary of Criterion Evidence

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses

Criterion		Synthesized Information
11	**Relative cost of the test**	According to our estimates, the cost of whole body bone scan with ^{99m}Tc-based radioisotopes is $278.70. ^{18}F-PET and ^{18}FDG-PET are significantly more costly alternatives.

Relative Costs

Test	Total costs ($)	Cost of Test Relative to ^{99m}Tc-based Test ($)
Whole body bone scan	278.70	Reference
^{18}F-PET	850.00	+571.30
^{18}FDG-PET	1050.00	+771.30

CT = computed tomography; ^{18}FDG-PET = 18-fluorodeoxyglucose positron emission tomography; mSv = millisievert; PET = positron emission tomography; ^{99m}Tc-MDP = ^{99m}technetium-labelled methylene diphosphonate; ^{99m}Tc = technetium-99m.

CRITERION 1: Size of affected population (link to definition)

Bone is a common site of metastasis, and the most common types of tumours to metastasize to bone are breast, prostate, lung, kidney, and thyroid.[34] The estimated numbers of new cases of breast, prostate, and lung cancer in 2011 are tabulated. Based on data from a population-based analysis of approximately 100,000 women with breast cancer and 125,000 men with prostate cancer, the incidence of bone metastasis at diagnosis or during follow-up (median 3.3 years) was 7.3%[16] and 7.7%,[17] respectively. Similar data were not available for lung cancer. Studies have reported an incidence of bone metastases of approximately 30% for patients with non–small cell lung cancer (NSCLC).[18] Using the estimated number of new cases reported by the Canadian Cancer Society (CCS) for 2011,[19] and these reported rates of metastasis, Table 2 reports the estimated number of cases of bone metastasis per 100,000 people.

Table 2: Cases of Bone Metastasis

Cancer Type	2011 Estimated Number of New Cases/100,000[19]	Estimated Number of Cases of Bone Metastasis per 100,000*
Breast	102† (0.102%)	7.4 (0.0074%)
Prostate	122 (0.122%)	9.4 (0.0094%)
Lung	57 (0.057%)	17.1 (0.0171%)

*Calculated from estimated new cases and the reported rates of bone metastasis for each type of cancer.[16-18]
†Females only.

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Imaging to detect bone metastases is needed to enable treatment planning and follow-up.[20] Pain and quality of life have been reported to improve in prostate cancer patients with bone metastasis who are treated with hormonal therapy or bisphosphonates.[20,35] In patients with breast cancer, detection of metastases may prevent complications and control disease progression.[7]

A study in patients with myxoid liposarcoma, which commonly metastasizes to the spine, reported the effects of treatment following detection of spinal metastasis.[36] Thirty-three patients with detected spinal metastasis were treated with either radiation alone (n = 8), surgery and radiation (n = 14), surgery alone (n = 4), or did not receive treatment (n = 7). Treatment with surgery and radiation improved pain scores in all patients with reported pain. In addition, two patients who were treated (one with surgery alone, one with surgery and radiation) were disease free at long-term follow-up. All patients who were untreated were either no longer alive, or alive with disease. This study concluded that diagnosis of bone metastasis and early treatment can improve outcomes such as controlling pain.

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Data from the 2011 Canadian Cancer Society Statistics reported that the estimated five-year relative survival ratio (for the period 2004 to 2006) is 88%, 96%, and 19% for breast, prostate, and lung cancer, respectively. Survival ratios are influenced significantly by the stage of disease.[19]

If an imaging test was not performed, staging information cannot be obtained and treatment cannot be appropriately planned. Diagnostic imaging test results can have a moderate impact on mortality.

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Bone metastasis has been reported to be associated with pain, hypercalcemia, nerve compression, fractures, and disability.[7,20,37] Detection and subsequent treatment of bone metastasis can improve outcomes such as pain and quality of life.

Imaging is required for accurate staging of disease and for selecting the appropriate treatment. Without accurate staging information, patients may receive less aggressive treatment (e.g., a patient with clinical stage I or II disease who would have been restaged to stage III as a result of imaging findings and, subsequently, managed differently) or more aggressive treatment (e.g., surgery being unnecessarily performed on a patient who would not benefit from it, based on diagnostic imaging information — for instance, if they had metastatic disease that has spread throughout the body, which would have been detected by imaging).

Diagnostic imaging test results can have a significant impact on morbidity or quality of life.

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CRITERION 5: Relative impact on health disparities (link to definition)

A 2005 study reported that diagnostic imaging tests were conducted more frequently in patients with a higher socioeconomic status than those with a lower socioeconomic status.[38]

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

Bone scanning
Patients, or parents of patients, may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. Limited information was identified on the acceptability of bone scanning to pediatric patients. A retrospective study on the use of bone scanning in children with osteosarcoma or Ewing sarcoma suggested that any test, including a bone scan, causes psychological strain on the children and the parents.[39]

^{18}F or ^{18}FDG-PET
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. Patients undergoing ^{18}FDG-PET are required to fast prior to the scan.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Based on the American College of Radiology Appropriateness Criteria,[40-42] the following whole body bone scans using ^{99m}Tc are "usually appropriate" or "may be appropriate" for the following indications:

Breast cancer
- Patients with stage II carcinoma who are presenting with back and hip pain
- Patients with known bone metastatic disease who are presenting with pathological fracture of left femur on x-ray

Prostate cancer
- Asymptomatic patients with nodule on physical exam determined to be poorly differentiated carcinoma and who have a prostate specific antigen (PSA) level greater or equal to 20 mg/mL

Lung cancer
- Patients with a 1 cm lung nodule determined to be non–small cell who are presenting for staging and resection
- Patients who are undergoing non-invasive staging of NSCLC. (Note: may be appropriate — not needed if PET scan was performed.)

See Appendix 3 for more information regarding the ACR Appropriateness Criteria applicable to bone tumour imaging.

Breast Cancer

For patients with breast cancer, three systematic reviews[5-7] and three observational studies[11,12,43] were included that compared the diagnostic accuracy of bone scan for detecting bone metastases with either ^{18}FDG-PET or ^{18}FDG-PET/CT.

Systematic reviews and meta-analyses
A 2011 systematic review and meta-analysis compared bone scan, ^{18}FDG-PET, and magnetic resonance imaging (MRI) for detection of bone metastasis.[5] Databases were searched between 1995 and 2010, without any restriction on language. Studies were included that used ^{18}FDG-PET, MRI, or bone scan with ^{99m}Tc-MDP to identify bone metastases in patients with breast cancer; used histopathological analysis or imaging and clinical follow-up as the reference standard; and reported per-patient or per-lesion data that could be used to calculate measures of diagnostic accuracy. Studies of children, case reports, letters, editorials, and reviews were excluded, as were studies that used radiopharmaceuticals other than ^{18}FDG or ^{99m}Tc-MDP (e.g., technetium-99m-hexakismethoxy-isobutyl-isonitril [^{99m}Tc-MIBI] bone scan). Quality of the included studies was assessed using the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) instrument and only those with a score of 9 or higher were included.

The study characteristics for included articles were not published. This information was requested, but not received. Table 3 reports the sensitivity and specificity of the imaging tests on a per-patient and per-lesion basis. The authors described the quality of the included studies as suboptimal, due to issues with the reference standard and blinding of the individuals interpreting images. Overall, the study concluded that on a per-patient basis, MRI was more effective at detecting bone metastases in breast cancer patients compared with ^{18}FDG-PET or bone scan, whereas ^{18}FDG-PET had lower sensitivity than bone scanning on a per-lesion basis. However, further information regarding the patient characteristics should be considered.

Table 3: Sensitivity and Specificity of Diagnostic Methods to Detect Bone Metastases in Patients with Breast Cancer[5]

Test	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	Patient Basis		Lesion Basis	
Bone scan	87.0 (82.1 to 90.9)	88.1 (84.6 to 91.0)	87.8 (83.9 to 91.1)	96.1 (94.7 to 97.2)
MRI	97.1 (90.1 to 99.7)	97.0 (89.5 to 99.6)	NS	NS
^{18}FDG-PET	83.3 (78.2 to 90.8)	94.5 (88.5 to 98.0)	52.7 (47.0 to 58.4)	99.6 (98.9 to 99.0)

CI = confidence interval; ^{18}FDG =18F fluorodeoxyglucose; MRI = magnetic resonance imaging; NS = no studies; PET = positron emission tomography.

In a 2010 systematic review, Escalona et al.[6] evaluated the use of ^{18}FDG-PET in breast cancer. One objective was to evaluate the accuracy of ^{18}FDG-PET in detecting metastases. Studies that compared the diagnostic accuracy of ^{18}FDG-PET with a reference test in patients with breast cancer were included. Health technology assessments, systematic reviews, meta-analyses, and observational and experimental studies were eligible for inclusion. Studies that included mixed cancer populations (in which data for breast cancer were not reported separately) were excluded. There was no limitation on the search time frame, which ran until February 2007. The quality of the included studies was assessed using a checklist for diagnostic studies.

In total, 73 studies were included in the systematic review, eight of which evaluated ^{18}FDG-PET compared with bone scan in the detection of bone metastases. A total of 382 patients were included across the eight studies. The quality of the included studies was described as low, due to small sample sizes, failure to report on blinding of the individual interpreting images, use of multiple PET scanners and provision of only aggregate results, and the inclusion of patients with different tumour stages without presenting results according to stage. The authors of the systematic review did not pool diagnostic accuracy data across studies and were unable to report results according to tumour stage, given the available data. No patient characteristics were reported for the individual studies, making it unclear as to whether patients were symptomatic or asymptomatic.

The sensitivity of both ^{18}FDG-PET and bone scan in detecting bone metastases ranged from 77.7% to 100%. The specificity of ^{18}FDG-PET ranged from 88.2% to 100%, while the specificity of bone scan ranged from 80% to 100%. The positive predictive value (PPV) and negative predictive value of ^{18}FDG-PET were reported in only one study, and were 85.7% and 95.8%, respectively, compared with 70.6% and 95.2%, respectively, for bone scan. Estimates of the accuracy of ^{18}FDG-PET ranged from 83.1% to 97.7% and 78.7% to 93.2% for bone scan. It was

unclear if the results presented were on a patient or lesion basis. The authors concluded that ^{18}FDG-PET appears to be more specific than bone scan in detecting bone metastases in patients with breast cancer, but should not be used in isolation.

Shie et al. published a systematic review and meta-analysis in 2008 comparing ^{18}FDG-PET and bone scans to detect bone metastasis.[7] Studies including breast cancer patients who underwent both ^{18}FDG-PET and bone scans within three months of one another, with positive finding confirmed by CT, MRI, or biopsy, were included. Patients of all stages were included (no breakdown was provided). In addition, it was not stated if the patients had symptoms of bone metastasis. Formal quality assessment of the included studies did not appear to be performed.

Six studies were included in the analysis. On a patient basis (184 patients from three studies), the pooled sensitivity was 81% for ^{18}FDG-PET and 78% for bone scan, and specificity was 93% for ^{18}FDG-PET and 79% for bone scan. On a lesion basis (1,207 patients from four studies), the sensitivity was 69% and 88%, and the specificity was 98% and 87% for ^{18}FDG-PET and bone scan, respectively. The authors concluded that it is unclear which modality is superior for detection of bone metastasis in patients with breast cancer, but ^{18}FDG-PET may be a more useful confirmatory test due to its higher specificity.

Observational studies
Two observational studies were identified that evaluated the diagnostic performance of bone scan relative to another imaging modality for the detection of bone metastases in patients with breast cancer.[11,12] These studies were not included in any of the three systematic reviews and are summarized individually in Tables 13 and 14 in Appendix 4. Bone scan with ^{99m}Tc-MDP was compared with ^{18}FDG-PET/CT[11] and ^{18}FDG-PET[12] (Appendix 4, Table 13). One study was a prospective cohort study[12] and the second was a retrospective cohort study.[11] Both studies were conducted in the United States. [11,12] It was unclear in either of the studies if the patients were symptomatic or asymptomatic, but patients in these studies were either high risk for metastases or were suspected of having metastases.[11,12]

Neither of the two studies reported outcomes according to cancer stage. In one study, the concordance between bone scan and ^{18}FDG-PET/CT was 81% (Appendix 4, Table 14).[11] Sensitivity and specificity were not reported in this study. In the second study, the sensitivity of conventional imaging (bone scan and CT) and ^{18}FDG-PET was equivalent (80%), while the specificity was greater with ^{18}FDG-PET than with conventional imaging (94% versus 79%).[12] Conclusions and limitations of the individual studies can be found in Appendix 4, Table 14.

Lung Cancer

For patients with lung cancer, one systematic review[8] and two observational studies[13,14] were included that compared the diagnostic accuracy of bone scan in detecting bone metastases with either ^{18}FDG-PET or ^{18}FDG-PET/CT.

Systematic reviews and meta-analyses
Bone scan, MRI, and ^{18}FDG-PET for detecting bone metastasis in patients with lung cancer were compared in a systematic review and meta-analysis published in 2011.[8] Databases were searched between 1995 and 2010, without any restriction on language. Studies were included that used ^{18}FDG-PET or bone scan with ^{99m}Tc-MDP to detect bone metastases in patients with lung cancer; reported per-patient or per-lesion data that could be used to calculate measures of diagnostic accuracy. Clinical follow-up, imaging follow-up, histopathological analysis, or radiographic confirmation were used as reference standards. Studies of children, case reports,

letters, editorials, and reviews were excluded, as were studies that used radiopharmaceuticals other than ^{18}FDG or ^{99m}Tc-MDP (e.g., ^{99m}Tc-MIBI bone scan). Quality of the included studies was assessed using the QUADAS instrument and only those with a score of 9 or higher were included. The study characteristics for included articles were not published. This information was requested, but not received.

Fourteen articles that in total reported data on 5,676 patients were included in the analysis. Issues with study quality were identified, mainly with regard to the reference standard and blinding of the individual interpreting images. Table 4 reports the sensitivity and specificity of the three modalities on a per-patient and per-lesion basis. ^{18}FDG-PET was reported to have better diagnostic accuracy than MRI or bone scanning. The authors concluded that ^{18}FDG-PET is superior for detecting bone metastasis in patients with lung cancer. However, further information regarding the patient characteristics should be considered.

Table 4: Sensitivity and Specificity of Diagnostic Methods to Detect Bone Metastasis in Lung Cancer[8]

Test	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	Patient Basis		Lesion Basis	
Bone scan	91.8 (89.1 to 94.1)	68.8 (65.8 to 71.6)	71.5 (66.9 to 75.8)	91.0 (89.2 to 92.7)
MRI	80.0 (67.0 to 89.6)	90.6 (85.8 to 94.3)	83.8 (77.0 to 89.2)	96.3 (95.3 to 97.1)
^{18}FDG-PET	91.9 (88.8 to 94.3)	96.8 (96.0 to 97.6)	95.0 (93.5 to 96.2)	94.6 (93.5 to 95.5)

CI = confidence interval; ^{18}FDG =18F fluorodeoxyglucose; MRI = magnetic resonance imaging; PET = positron emission tomography.

Observational studies

Two observational studies, one in patients with NSCLC and one in patients with small cell lung cancer (SCLC), were identified that evaluated the diagnostic performance of bone scan relative to ^{18}FDG-PET[13] or ^{18}FDG-PET/CT[14] for preoperative staging. These studies are summarized in Tables 13 and 14 in Appendix 4. Bone scan was performed with ^{99m}Tc-labelled oxydronate in one study,[14] while the radiopharmaceutical used in the other study was not specified.[13] Both studies used prospective cohort designs. One was conducted in Italy[13] and one was conducted in Denmark.[14] It was unclear if patients in the two studies were symptomatic or asymptomatic.

Outcomes were not reported according to cancer stage. In patients with NSCLC, the sensitivity of bone scan was 67% compared with 96% with ^{18}FDG-PET, while the specificity of bone scan was 94% compared with 99% with ^{18}FDG-PET. For patients with SCLC, the sensitivity of bone scan was 75% but was not reported for ^{18}FDG-PET/CT.[14] In 17% of patients, ^{18}FDG-PET/CT suggested a different stage than conventional staging.[14] Conclusions and limitations of the individual studies can be found in Appendix 4, Table 14.

Prostate Cancer

Observational studies
One US-based prospective cohort observational study was identified that evaluated the diagnostic performance of bone scan relative to ^{18}FDG-PET for the detection of bone metastases in patients with prostate cancer.[15] Further information on this study is available in Tables 13 and 14 in Appendix 4.

Outcomes were not reported according to cancer stage. The authors reported that ^{18}FDG-PET/CT detected bone metastases in 72.1% of patients compared with 86.1% with bone scan (P = 0.01) (Appendix 4, Table 14).[15] Conclusions and limitations can be found in Appendix 4, Table 14.

Studies Involving Multiple Cancer Types

A systematic review and meta-analysis published in 2011 compared ^{18}FDG-PET/CT with bone scintigraphy in the detection of bone metastases in patients with malignancies.[9] English-language studies published between 2000 and 2010 were eligible for inclusion if they compared ^{8}FDG-PET/CT with bone scan in patients of any age or disease stage; presented sufficient data to calculate measures of diagnostic accuracy; used histopathological follow-up, clinical follow-up, and/or combined imaging as the reference test; and reported on at least six patients. Study quality was assessed using the QUADAS instrument.

Six studies involving a total of 1,560 patients were included in the meta-analysis. Three studies were prospective and three were retrospective. Patient-based data were reported in five studies, while lesion-based data were reported in one. Three studies included only patients with NSCLC, one study included patients with either NSCLC or SCLC, one study included patients with nasopharyngeal cancer, and one study included patients with Ewing sarcoma, ganglioneuroblastoma, rhabdomyosarcoma, neuroblastoma, or granulocytic sarcoma. Of the 1,560 patients, 1,341 had NSCLC. Details on cancer stage or whether patients were symptomatic were not reported.

The authors described all studies as being of moderate quality and reported that the main weakness in the included studies involved the reference standard, which was not independent of the index test or not the same for all patients. Table 5 reports the sensitivity and specificity of the imaging methods on a per-patient basis. The authors concluded that the pooled sensitivity and specificity of ^{18}FDG-PET/CT were higher than bone scan, but that further research was required to evaluate ^{18}FDG-PET/CT in other malignancies such as breast and prostate cancer.

Table 5: Sensitivity and Specificity of Diagnostic Methods to Detect Bone Metastasis [9]

Test	Sensitivity (95% CI)	Specificity (95% CI)
Bone scan	0.71 (0.64 to 0.76)	0.91 (0.90 to 0.93)
^{18}FDG-PET/CT	0.93 (0.89 to 0.96)	0.98 (0.97 to 0.98)

CI = confidence interval; ^{8}FDG = 18F fluorodeoxyglucose; PET/CT = positron emission tomography/computed tomography.

A systematic review and meta-analysis published in 2010[10] reported the diagnostic accuracy of ^{18}FDG-PET, ^{18}FDG-PET/CT, bone scan, and bone scan plus single-photon emission computed tomography (SPECT) for detecting bone metastasis. Eleven studies involving 425 patients were included in the analysis and studies were characterized based on whether patients were analyzed on a patient basis (350 patients) or a lesion basis (255 patients). The population included patients with lung cancer, prostate cancer, breast cancer, and hepatocellular carcinoma, and it was not reported in six of the included studies. The reference standard varied across the 11 studies, and included CT, MRI, radiography, ^{18}FDG-PET, clinical follow-up, or biopsy. Table 6 reports the sensitivity and specificity of the imaging methods. Some studies combined the findings from PET and PET/CT or bone scan and bone scan plus SPECT. Only the results of the individual tests are included in Table 6.

Table 6: Sensitivity and Specificity of Diagnostic Methods to Detect Bone Metastasis[10]

Test	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
	Patient Basis		Lesion Basis	
BS	0.468 (0.398 to 0.537)	0.883 (0.829 to 0.936)	0.579 (0.526 to 0.632)	0.954 (0.924 to 0.984)
BS + SPECT	0.815 (0.706 to 0.923)	0.990 (0.973 to 1.000)	0.357 (0.198 to 0.516)	0.961 (0.921 to 1.000)
^{18}FDG-PET	0.949 (0.912 to 0.986)	0.987 (0.972 to 1.000)	0.958 (0.942 to 0.974)	0.983 (0.969 to 0.996)
^{18}FDG-PET/CT	0.977 (0.938 to 1.000)	0.959 (0.905 to 1.000)	0.978 (0.964 to 0.991)	0.978 (0.966 to 0.990)

BS = bone scan; CI = confidence interval; CT = computed tomography; ^{18}FDG =18F fluorodeoxyglucose; PET = positron emission tomography; SPECT = single-photon emission computed tomography.

Overall, the sensitivity and specificity of ^{18}FDG-PET and ^{18}FDG-PET/CT were higher for detection of bone metastasis compared with bone scan with or without SPECT. The authors concluded that ^{18}FDG-PET or PET/CT can be substituted for bone scanning with ^{99m}Tc during a supply shortage. The radiation dose was reported to be higher for ^{18}FDG-PET and PET/CT (range: 2.7 to 28 mSv) than bone scans (range: 4.2 to 5.7 mSv), and therefore should be a consideration. A major limitation of this report is that it was not stated whether the patients with known cancer were symptomatic/asymptomatic or if imaging was being conducted for staging purposes. The list of included studies evaluated patient populations that are likely very different. For example, one study evaluated bone imaging in high-risk prostate cancer patients and another in newly diagnosed lung cancer patients.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non-radiation Risks

Bone scanning
Several studies[44-47] reported mild adverse events with ^{99m}Tc-labelled tracers (e.g., skin reactions) and one case report published in 1985 reported a patient who experienced a rash following two bone scans with ^{99m}Tc-MDP, one in 1983 and one the following year.[23] The authors concluded this patient had an allergic reaction to MDP on both occasions. This case report references an older study that reported 22 adverse reactions to ^{99m}Tc-MDP, in which 20 of the reactions were either "probably" or "possibly" caused by MDP.

PET
The Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[48]

Radiation Exposure

Among the modalities available for bone tumour imaging, bone scanning and PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures is shown in Table 7. For comparison, the average effective dose of natural background radiation to which individuals are exposed over a year duration is 3.0 mSv.[28]

The radiation dose reported in the systematic review by Tateishi et al. was lower for bone scans (4.2 to 5.7 mSv) than ^{18}FDG-PET and PET/CT (2.7 to 28 mSv).[10] Another study reported that the calculated dose of radiation for a bone scan is 5 to 6 mSv.[39]

Table 7: Effective Doses of Radiation[24,25]

Procedure	Average Effective Dose (mSv)
Bone scan	6.3
Whole body PET	14.1
Average background dose of radiation per year	1 to 3.0[26-28]

CT = computed tomography; mSv = millisievert; PET = positron emission tomography.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

Expertise

Reliability of the interpretation of bone scans (or other diagnostic imaging tests) by different readers (interobserver agreement) is routinely assessed using the kappa (Ķ) score — a measure of agreement beyond that expected by chance alone.[49] A kappa score of less than 0.20 means poor agreement, 0.21 to 0.40 fair agreement, 0.41 to 0.60 moderate agreement, 0.61 to 0.80 good agreement, and 0.81 to 1.00 very good agreement.[50]

Interobserver agreement of bone scans was compared in a retrospective study published in 2008 of 59 breast and prostate cancer patients.[29] Thirty-seven physicians with daily experience

in reading bone scans were involved in the study. Clinical examination (including bone scan results, laboratory results, other diagnostic tests, and follow-up examination) of all patients by the same experienced physician was used as the gold standard. Pairwise comparisons between two different examiners were calculated for 666 pairs. The mean kappa coefficient between the observers was 0.48, which is classified as a "moderate" level of agreement. The mean kappa coefficient for inexperienced observers compared with the gold standard was 0.40, and the moderately experienced and experienced observers had a mean kappa coefficient of 0.51.

Interobserver agreement was also reported in the study by Balliu et al.[30] The agreement between two observers for bone scanning was low for a four-point scale (kappa index = 0.260) but moderate on a two-point scale (kappa index = 0.524). Takenaka et al.[31] also reported interobserver agreement between tests. The kappa index was 0.67 for bone scanning and 0.65 for ^{18}FDG-PET/CT, indicating substantial agreement with either test.

Personnel

Bone scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of bone scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging.[51] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct bone scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted part-time) should be available for the installation, testing, and ongoing quality control of nuclear medicine equipment.[51]

PET
In Canada, physicians involved in the performance, supervision, and interpretation of PET scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Technologists must be certified by CAMRT or an equivalent licensing body.

A summary of the availability of personnel required for the conduct of bone tumour imaging, by bone scanning or any of the alternative imaging modalities, is provided in Table 8.

Table 8: Medical Imaging Professionals in Canada[52]				
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**Nuclear Medicine Technologists**	**Medical Physicists**
NL	46	3	15	NR
NS	71	5	71	NR
NB	47	3	55	NR
PEI	7	0	3	0
QC	522	90	460	NR
ON	754	69	693	NR
MB	58	8	42	NR
SK	61	4	36	NR
AB	227	18	193	NR
BC	241	21	212	NR
YT	0	0	0	0
NWT	0	0	1	0
NU	0	0	0	0
Total	**2,034**	**221**	**1,781**	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdictions; NS = Nova Scotia; NU = Nunavut; NWT= Northwest Territories; ON = Ontario; PEI = Prince Edward Island; QC = Quebec; YT = Yukon.
*This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

Wait Times

Wait-time benchmarks were reported by the Canadian Medical Association for the Wait Time Alliance (WTA) in 2005.[21] For bone scanning and ^{18}FDG-PET, the wait-time benchmark was immediate to 24 hours for an emergency case, within seven days for an urgent case, and within 30 days for a scheduled case. The WTA reported wait times for urgent bone scan as ranging from one to six days throughout the provinces, and for scheduled cases, the range was seven to 73 days.[32]

Equipment

There are notable variations in the availability of medical imaging technologies within hospitals across Canada. Nuclear medicine cameras are not available in the Yukon, the Northwest Territories, and Nunavut. Table 9 provides an overview of the availability of equipment required to imaging bone metastases. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010.

Bone scanning
For bone scintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[52]

PET

A 2010 Environmental Scan published by CADTH reported that approximately 31 Canadian centres are equipped to perform PET scans.[33] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[33] There are 36 PET or PET/CT scanners, four of which are used for research purposes only.[33]

Table 9: Diagnostic Imaging Equipment in Canada[33,52,53]

	Nuclear Medicine Cameras	SPECT/CT Scanners	PET or PET/CT Scanners
Number of devices	603[52]	96[53]	36[33]
Average number of hours of operation per week (2006-2007)[52]	40	NA	NA
Provinces and Territories with no devices available	YT, NT, NU	PEI, YT, NT, NU	NL, PEI, SK, YT, NT, NU

NA = not available; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; YT = Yukon.

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of bone scanning and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 10), the cost of whole body bone scan with ^{99m}Tc-based radioisotopes is $278.70. ^{18}F-PET and ^{18}FDG-PET are significantly more costly alternatives.

Table 10: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[54]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
Whole Body Bone Scan				
J850	Bone scintigraphy — general survey	106.35	62.80	169.15
J866	Application of tomography (SPECT), maximum one per nuclear medicine examination	44.60	31.10	75.70
Maintenance fees — global budget		33.85		33.85
	TOTAL	184.80	93.90	**278.70**
^{18}F-PET				
J706	NSCLC		250.00	250.00
Technical cost — from global budget		600.00		600.00
	TOTAL	600.00	250.00	**850.00**

Table 10: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[54]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
^{18}FDG-PET				
J706	NSCLC		250.00	250.00
Technical cost — from global budget		800.00		800.00
	TOTAL	800.00	250.00	**1,050.00**

CT = computed tomography; ^{18}F = 18F-fluoride; ^{18}FDG = 18F-fluorodeoxyglucose; NSCLC = non–small cell lung cancer; PET = position emission tomography; prof = professional; SPECT = single-photon emission computed tomography; tech. = technical.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criteria	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales, with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criteria	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the technetium-99m (^{99m}Tc)-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criteria	**Definition**
	criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared to alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 2011 EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2011 EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011 EBM Reviews - Health Technology Assessment 1st Quarter 2011 EBM Reviews - NHS Economic Evaluation Database 1st Quarter 2011 **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	March 14, 2011
Alerts:	Monthly search updates began March 14, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	English language Humans No date limits for systematic reviews; publication years Jan 2006 to March 2011 for primary studies.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Multi-database Strategy

#	Searches
	Bone tumours concept
1	exp Bone Neoplasms/
2	exp Neoplasms, Bone Tissue/
3	Chondrosarcoma/
4	Bone Marrow Neoplasms/
5	((bone or bony or skeletal* or skeleton* or spine or spines or spinal or orbital* or skull* or nose or nasal or jaw or jaws or maxillary or mandible or femoral* or femur or saccrococcygeal or sacroccyx or osseus or osteolytic or osteoblastic or osteoid) adj3 (metastatic or metastases or metastasis or neoplasm* or cancer* or tumor* or tumour* or malignanc* or carcinoma* or sarcoma*)).ti,ab.
6	(osteosarcoma* or osteogenic sarcoma*).ti,ab.
7	MBD.ti,ab.
8	(chondrosarcoma* or Ewing* sarcoma* or ESFT? or chordoma* or adamantinoma*).ti,ab.
9	(osteoma* or osteochondroma* or osteoblastoma*).ti,ab.
10	or/1-9
	Radionuclide imaging concept
11	Technetium/ or exp Technetium Compounds/ or exp Organotechnetium Compounds/ or exp Radiopharmaceuticals/
12	Radionuclide Imaging/
13	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).ti,ab,nm.
14	radioisotope*.ti,ab.
15	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
16	Tomography, Emission-Computed, Single-Photon/
17	(single-photon adj2 emission*).ti,ab.
18	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
19	exp Bone Neoplasms/ri
20	exp "Bone and Bones"/ri
21	Technetium Tc 99m Medronate/
22	(medronate or methyl diphosphonate).ti,ab.
23	((bone or MDP) adj2 (imaging or scan*)).ti.
24	or/11-23
25	10 and 24
	Filter: human studies
26	exp animals/
27	exp animal experimentation/

Multi-database Strategy	
28	exp models animal/
29	exp animal experiment/
30	nonhuman/
31	exp vertebrate/
32	animal.po.
33	or/26-32
34	exp humans/
35	exp human experiment/
36	human.po.
37	or/34-36
38	33 not 37
39	(comment or newspaper article or editorial or letter or note).pt.
40	25 not (38 or 39)
	Filter: randomized controlled trials, non-randomized studies, diagnostic accuracy
41	Randomized Controlled Trial.pt.
42	Controlled Clinical Trial.pt.
43	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
44	Multicenter Study.pt.
45	(random* or sham or placebo*).ti.
46	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
47	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
48	(control* adj3 (study or studies or trial*)).ti.
49	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
50	(allocated adj "to").ti.
51	Cohort Studies/
52	Longitudinal Studies/
53	Prospective Studies/
54	Follow-Up Studies/
55	Retrospective Studies/
56	Case-Control Studies/
57	Cross-Sectional Study/
58	(observational adj3 (study or studies or design or analysis or analyses)).ti.
59	cohort.ti.
60	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
61	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.

Multi-database Strategy	
62	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
63	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
64	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
65	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
66	(population adj3 (study or studies or analysis or analyses)).ti.
67	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
68	Comparative Study.pt.
69	(Validation Studies or Evaluation Studies).pt.
70	exp "Sensitivity and Specificity"/
71	False Positive Reactions/
72	False Negative Reactions/
73	(sensitivit* or distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti.
74	(predictive adj4 value*).ti,ab.
75	or/41-74
76	75 not case reports.pt.
77	40 and 76
	Results: primary studies
78	limit 77 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]
79	limit 78 to yr="2006 -Current" [Limit not valid in DARE; records were retained]
80	remove duplicates from 79
	Filter: health technology assessments, systematic reviews, meta-analyses
81	meta-analysis.pt.
82	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
83	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
84	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
85	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
86	(data synthes* or data extraction* or data abstraction*).ti,ab.
87	(handsearch* or hand search*).ti,ab.
88	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.

Multi-database Strategy	
89	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
90	(meta regression* or metaregression* or mega regression*).ti,ab.
91	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
92	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
93	(cochrane or health technology assessment or evidence report).jw.
94	(meta-analysis or systematic review).md.
95	or/81-94
96	40 and 95
	Results: health technology assessments, systematic reviews, meta-analyses
97	limit 96 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]
98	remove duplicates from 97

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 10 to 18, 2011
Keywords:	Included terms for bone cancer, bone tumours, and diagnostic imaging
Limits:	Focus on publication years 2005 to present.

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters), were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: ACR Appropriateness Criteria[40-42]

The American College of Radiology (ACR) uses a modified Delphi process to reach its appropriateness criteria. ACR authors first review relevant information and create a summary. This summary is reviewed by clinicians and other medical professionals. The process allows for the incorporation of expert consensus when published evidence is lacking. A panel of experts rates the information to determine appropriateness of the imaging intervention.

Appropriateness is rated between 1 and 9 and is grouped into three categories: "usually not appropriate" (scores of 1, 2, and 3) or as not indicated in a certain clinical setting and unlikely to have a favourable risk-benefit ratio for patients; "maybe appropriate" (scores of 4, 5, and 6) or as potentially indicated in certain clinical settings and having potential to have an equivocal risk-benefit for patients; and "usually appropriate" (scores of 7, 8, and 9) or as indicated in certain clinical settings and having a favourable risk-benefit ratio for patients. All ratings are based on peer-reviewed literature and the opinions of the expert panel. The expert panel must reach consensus (defined as 80% agreement) after three rounds of scoring before the ACR appropriateness scores are finalized.

Table 12: American College of Radiology Appropriateness Criteria

Breast Cancer	
Type: Stage I carcinoma — initial presentation is asymptomatic	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 1 ("usually not appropriate")
Myelography and post-myelography CT spine	Rating = 1 ("usually not appropriate")
MRI with or without contrast — area of interest	Rating = 1 ("usually not appropriate")
^{18}FDG-PET scan — whole body	Rating = 1 ("usually not appropriate")
Type: Stage I carcinoma — purpose is to rule out bone metastases	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 2 ("usually not appropriate")
^{18}FDG-PET scan — whole body	Rating = 2 ("usually not appropriate")
Type: Stage II carcinoma — presenting with back and hip pain	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 9 ("usually appropriate")
^{99m}Tc bone scan (with SPECT) — hip and spine	Rating = 1 ("usually not appropriate")
Myelography and post-myelography CT spine	Rating = 1 ("usually not appropriate")
CT (with or without contrast) — hip and spine	Rating = 1 ("usually not appropriate")
MRI (with or without contrast) — hip and spine	Rating = 1 ("usually not appropriate")
^{18}FDG-PET scan — whole body	Rating = 5 ("may be appropriate")
Type: Known bone metastatic disease — presenting with pathological fracture of left femur on x-ray	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 9 ("usually appropriate")
^{18}FDG-PET scan — whole body	Rating = 5 ("may be appropriate"); if bone scan is negative, findings on PET will influence the use of systemic treatment.
CT without contrast — femur	Rating = 1 ("usually not appropriate")
MRI without contrast — femur	Rating = 1 ("usually not appropriate")

Table 12: American College of Radiology Appropriateness Criteria

Prostate Cancer	
Type: Nodule on physical exam; moderately or well-differentiated carcinoma; PSA < 20mg/mL; asymptomatic patients	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 1 ("usually not appropriate")
CT with or without contrast — area of interest	Rating = 1 ("usually not appropriate")
MRI with or without contrast — area of interest	Rating = 1 ("usually not appropriate")
^{18}FDG-PET scan — whole body	Rating = 1 ("usually not appropriate")
Type: Nodule on physical exam; poorly differentiated carcinoma; PSA ≥ 20mg/mL; asymptomatic patients	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 9 ("usually appropriate")
CT with or without contrast — area of interest	Rating = 1 ("usually not appropriate")
MRI with or without contrast — area of interest	Rating = 1 ("usually not appropriate")
^{18}FDG-PET scan — whole body	Rating = 1 ("usually not appropriate")

Lung Cancer	
Type: 1 cm lung nodule; NSCLC at needle biopsy — presenting for staging and resection	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 9 ("usually appropriate"); not needed if a PET scan is performed for initial nodule workup.
^{18}FDG-PET scan — whole body	Rating = 9 ("usually appropriate")
CT without contrast — chest	Rating = 1 ("usually not appropriate")
MRI without contrast — chest	Rating = 1 ("usually not appropriate")
Type: Non-invasive staging of NSCLC	
Modality	**Rating and comments**
^{99m}Tc bone scan — whole body	Rating = 5 ("may be appropriate"); not needed if a PET scan has been performed
^{18}FDG-PET scan — skull base to mid-thigh	Rating = 9 ("usually appropriate"); attenuation correction by radionuclide or CT
CT with or without contrast — chest	Rating = 9 ("usually appropriate"); contrast is preferred if not contraindicated
CT with contrast —abdomen	Rating = 5 ("may be appropriate"); contrast is preferred if not contraindicated
CT with contrast — head	Rating = 5 ("may be appropriate"); used if MRI is contraindicated and the patient has neurological symptoms
MRI with or without contrast — head	Rating = 7 ("usually appropriate"); if the patient has neurological symptoms; or if the patient is asymptomatic, but the tumour is > 3 cm and has adenocarcinoma histology or mediastinal adenopathy
MRI with or without contrast — chest	Rating = 3 ("usually appropriate"); evaluating chest wall or cardiac invasion and for local staging of superior sulcus tumours.

CT = computed tomography; ^{18}FDG = 18F-fluorodeoxyglucose; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; PET = positron emission tomography; PSA = prostate-specific antigen; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m.

Appendix 4: Study Details

Table 13: Objective and Details of Study Design of the Included Primary Studies

Study	Objective	Population	Intervention and Comparator	Study Design	Location
Breast Cancer					
Morris et al. 2010[11]	To compare the diagnostic performance of BS and PET/CT in women with suspected metastatic breast cancer	All women undergoing evaluation of suspected metastatic breast cancer between 2003 and 2008 Excluded patients with a previous history of metastatic breast cancer or active secondary malignancy	Intervention: whole body bone scan with ^{99m}Tc-MDP Comparator: PET/CT from mid-skull to upper thighs	Retrospective cohort	Single centre in the United States
Port et al. 2006[12]	To determine the utility of FDG-PET compared with conventional imaging in evaluating the extent of disease in patients with high-risk, operable breast cancer	Patients who presented for operative treatment of breast cancer between 2001 and 2004 who had high-risk disease, defined as: Tumour size > 5 cm (T3) and/or clinically positive lymph nodes (N1/2)	Intervention: whole body bone scan with ^{99m}Tc-MDP and CT of the chest, abdomen, and pelvis (conventional imaging) Comparator: FDG-PET	Prospective cohort	Single centre in the United States
Lung Cancer					
Nosotti et al. 2008[13]	To compare preoperative staging using PET and conventional imaging technologies	Patients with proven or strongly suspected lung cancer referred to a thoracic surgery unit between 1999 and 2004 Proven NSCLC, pulmonary mass positive to PET, no history of previous cancer, no history of severe diabetes mellitus	Intervention: bone scan (radiopharmaceutical not identified) Comparator: whole body FDG-PET	Prospective cohort	Single centre in Italy

Table 13: Objective and Details of Study Design of the Included Primary Studies					
Study	**Objective**	**Population**	**Intervention and Comparator**	**Study Design**	**Location**
Fischer et al. 2007[14]	To examine PET/CT compared with conventional staging in patients with SCLC	Patients older than 18 years with histological or cytological proven SCLC were enrolled between 2003 and 2004 Patients with type 1 diabetes mellitus, known former or current malignancy other than SCLC, claustrophobia, pregnancy	Intervention: whole body bone scan with ^{99m}Tc oxydronate, bone marrow analysis, and CT scan Comparator: PET/CT (FDG-PET) from head to upper thigh	Prospective cohort	Denmark Number of centres not reported
Prostate					
Meirelles et al. 2010[15]	To evaluate BS and FDG-PET in patients with progressing metastatic prostate cancer	Patients with progressive prostate cancer who were enrolled in a prospective study between 1997 and 2000 Included those with at least 5 years of follow-up with histologically proven adenocarcinoma of the prostate and progression of disease as indicated from increasing PSA and an abnormality on imaging with BS, CT, or MRI that was consistent with bone metastases	Intervention: bone scan with ^{99m}Tc-MDP Comparator: whole-body FDG-PET	Prospective	United States Number of centres not reported

BS = bone scan; CT = computed tomography; ^{18}FDG =18F fluorodeoxyglucose; MRI = magnetic resonance imaging; NSCLC = non–small cell lung cancer; NS = no studies; PSA = prostate specific antigen; PET = positron emission tomography; SCLC = small cell lung cancer; T = tesla; ^{99m}Tc = technetium-99m; ^{99m}Tc-MDP = technetium-99m–labelled methylene diphosphonate.

Table 14: Patient Characteristics, Diagnostic Accuracy, Conclusions, and Limitations of the Included Primary Studies				
Study	**Patient Characteristics**	**Diagnostic Accuracy**	**Conclusions**	**Limitations**
Breast Cancer				
Morris et al. 2010[11]	N = 163 Suspicious symptoms: 84% Stages I to III breast cancer diagnosed > 12 weeks prior to imaging: 58% Estrogen receptor positive: 55% Progesterone receptor positive: 41% HER2 positive: 24%	Concordance between BS and ^{18}FDG-PET/CT: 81% (132 of 163 studies) For the 31 patients with discordant findings: 18 had positive ^{18}FDG-PET/CT and negative BS 2 had negative ^{18}FDG-PET/CT and positive BS The remaining 11 patients had equivocal findings on one of the imaging techniques	There is a high degree of concordance between imaging techniques, suggesting that they could be redundant. ^{18}FDG-PET/CT may be superior to BS for detecting metastases in patients with breast cancer.	Only patients who underwent both imaging modalities were included, which could limit the generalizability of the findings. ^{18}FDG-PET/CT was reserved for patients with diagnostic uncertainty, which could also affect the generalizability of the findings. No analysis according to stage Sensitivity and specificity were not computed. Single-centre study Authors stated that their sample reflected a subgroup of patients with breast cancer.
Port et al. 2006[12]	N = 80 Histological characteristics: Ductal: 78.8% Lobular: 7.5% Unknown/other: 13.8% Clinical stage at presentation:	Sensitivity: Conventional imaging — 80% ^{18}FDG-PET — 80% Specificity: Conventional imaging — 79% ^{18}FDG-PET — 94%	The use of PET for determining the extent of disease in patients with breast cancer may be appropriate in selected patients at high risk for having relevant findings.	BS was in combination with CT No analysis according to stage Did not report whether patients were symptomatic Some scans were performed at outside

Table 14: Patient Characteristics, Diagnostic Accuracy, Conclusions, and Limitations of the Included Primary Studies				
Study	**Patient Characteristics**	**Diagnostic Accuracy**	**Conclusions**	**Limitations**
	IIB: 50% Occult primary: 8.8% IIIA: 26.2% Locoregional recurrence: 15.0% Node status: Positive: 83.6% Negative: 16.4%			facilities, not the study centre Single staff radiologist interpreted the images, which could affect generalizability. Single-centre study Did not report results according to stage of cancer.
Lung Cancer				
Nosotti et al. 2008[13]	N = 413 Adenocarcinoma — 64.8% Squamous cell carcinoma: 30.2% Large cell carcinoma: 5%	Sensitivity: BS — 67% ^{18} FDG-PET — 96% Specificity: BS — 94% ^{18} FDG-PET — 99% PPV: BS — 64% ^{18} FDG-PET — 98% NPV: BS — 95% ^{18} FDG-PET — 99%	PET imaging strategy is more accurate than conventional imaging for the detection of metastases.	Few patient characteristics reported. Unclear if patients were symptomatic or asymptomatic Single-centre study No information on the radiopharmaceutical used for the bone scan. No information about image interpretation or blinding of the individual(s) interpreting images was reported. Did not report results according to stage of cancer.

Table 14: Patient Characteristics, Diagnostic Accuracy, Conclusions, and Limitations of the Included Primary Studies				
Study	**Patient Characteristics**	**Diagnostic Accuracy**	**Conclusions**	**Limitations**
Fischer et al. 2007[14]	N = 29 Final stage: Limited disease — 24% Extensive disease — 59% Undetermined — 18%	Sensitivity for bone metastases: BS — 75% ^{18}FDG-PET/CT — 80% Specificity for bone metastases: BS — 58% ^{18}FDG-PET/CT — not reported ^{18}FDG-PET/CT suggested a different stage than conventional staging in 17% of patients (n = 5)	There is most likely a role for ^{18}FDG-PET/CT in the staging of SCLC, but larger trials are needed before conclusions can be made.	Few patient characteristics reported. Unclear if patients were symptomatic or asymptomatic Specificity of ^{18}FDG-PET/CT for bone metastases not reported Sample size of 29 patients Unclear how patients were selected for inclusion (i.e., if all patients who reported for staging during the study period were included or whether the study involved a selected population). Did not report results according to stage of cancer.
Prostate				
Meirelles et al. 2010[15]	N = 51 Castrate-resistant disease: 76% No other characteristics reported	BS detected bone metastases in significantly (P = 0.01) more patients than ^{18}FDG-PET. Detection of metastases: BS: 86.1% ^{18}FDG-PET: 72.1%	In patients with progressing prostate cancer, bone metastases are readily identifiable on ^{18}FDG-PET.	Unclear if the same radiologist and nuclear medicine physician interpreted all images. Did not report sensitivity and specificity. Limited patient characteristics reported.

Table 14: Patient Characteristics, Diagnostic Accuracy, Conclusions, and Limitations of the Included Primary Studies				
Study	**Patient Characteristics**	**Diagnostic Accuracy**	**Conclusions**	**Limitations**
		Discordance between techniques: ^{18}FDG-PET positive, BS negative: 0% ^{18}FDG-PET negative, BS positive: 14%		Did not report results according to stage of cancer. High risk patients — could potentially limit generalizability to other patients with prostate cancer.

BS = bone scan; CT = computed tomography; ^{18}FDG =18F fluorodeoxyglucose; HER2 = Human Epidermal Growth Factor Receptor 2; MRI = magnetic resonance imaging; NPV = negative predictive value; NSCLC = non–small cell lung cancer; NS = no studies; PET = positron emission tomography; PPV = positive predictive value; PSA = prostate specific antigen; SCLC = small cell lung cancer.

APPENDIX 2.7

INDICATION OVERVIEW

According to the International Classification of Diseases (ICD), myocardial infarction (MI) — also known as acute myocardial infarction (AMI) or a heart attack, acute coronary syndrome (ACS), angina pectoris, and other forms of coronary heart disease (CHD) are all classified as ischemic heart disease (IHD).[1] An AMI occurs when a coronary plaque ruptures, causing a blood clot which may partially or completely block blood flow to the downstream heart muscle.[2] Lack of blood flow results in the death of cardiac muscle cells. Blood flow has to be restored promptly to prevent further loss of cardiac muscle cells.

Prognosis following MI depends on a number of factors including geographic location, patient's health, extent of heart damage, and treatment given.[3,4] Early risk stratification post-MI is important to determine patients at increased risk for a recurrent ischemic event and those at increased risk for cardiac death (arrhythmic or non-arrhythmic). Imaging allows for in-hospital assessment of prognosis and may guide patient post-MI management. If a patient is at high-risk for another event, treatment planning will likely be more aggressive and include invasive coronary angiography and possibly coronary revascularization.

Population: Patients who have been diagnosed with myocardial infarction.

Intervention: Myocardial perfusion imaging (MPI) using single-photon emission computed tomography (SPECT) using technetium-99m (^{99m}Tc)-labelled radiotracers.

During MPI, the radiopharmaceutical is taken up by the myocardium in proportion to regional blood flow. At rest, regional blood flow is similar in both stenotic and non-stenotic arteries. During stress by either exercise or pharmacological stressors (vasodilators or dobutamine) in the presence of coronary stenosis, the myocardium region supplied by the stenotic artery receives less coronary blood flow, resulting in less uptake of the radiopharmaceutical and an observed perfusion defect. The resulting image using ^{99m}Tc-labelled radiotracer SPECT provides information regarding infarct size and residual myocardium at risk, and allows for the calculation of an ejection fraction.[5] Infarct size, myocardium at risk, and left ventricular ejection fraction are predictors of mortality.[6]

Comparators: For this report, the following diagnostic tests are considered as alternatives to ^{99m}Tc-labelled radiotracer SPECT:

- *Computed tomography (CT) coronary angiography*
- *Stress echocardiogram (Echo)*
- *Stress magnetic resonance imaging (MRI)*
- *Stress positron emission tomography (PET)*
- *Stress ^{201}thallium SPECT (^{201}Tl-SPECT).*

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and myocardial infarction.

Methodological search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and controlled clinical trials, including diagnostic accuracy studies. Where possible, retrieval was limited to the human population. The literature search was also limited to the English language. No date limits were applied for the systematic review search. The primary studies search was limited to documents published between January 1, 2006 and February 24, 2011. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

Forty-six potential HTA, SR, and MA articles were identified and 11 were subjected to full text review. There were no MAs of the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT head-to-head comparisons with any comparator.

There were 480 primary study articles identified of which 44 were subjected to full-text screening. Two studies identified in the primary literature search evaluated the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus its comparators in the assessment of prognosis post-MI: one comparing ^{99m}Tc-labelled radiotracer SPECT with echo and MRI[7] and one comparing ^{99m}Tc-labelled radiotracer SPECT with MRI.[8] One additional study,[9] comparing the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT and rubidium-82 (^{82}Rb) PET in a broader patient population, was also included. No studies comparing ^{99m}Tc-labelled radiotracer SPECT with CT or ^{201}TI-labelled radiotracer SPECT met the inclusion criteria.

Two guidelines of interest were identified in the grey literature search: the American College of Cardiology (ACC) /American Heart Association (AHA) guidelines for the management of patients with ST-segment elevation myocardial infarction (STEMI)[10] and those for patients with non-STEMI (NSTEMI).[11]

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	There were 60,996 hospitalizations due to heart attacks in the 2006/2007 fiscal year (crude rate: 188.2 per 100,000 people).[12] 66,707 Canadians were hospitalized for a heart attack in the 2008/2009 fiscal year (age-standardized rate: 217 per 100,000 adults, 20 years of age or older).[13] Myocardial infarction (MI) rates vary across the country; however, the rate is lowest in Nunuvat (112/100,000; range: 49 to 176) and highest in Newfoundland and Labrador (347/100,000; range: 330 to 363).[13] The size of the affected population is more than 1 in 1,000 (0.1%) and less than or equal to 1 in 100 (1%).
2	**Timeliness and urgency of test results in planning patient management**	A delay in the revascularization process may result in irreversible damage to the myocardium and is associated with an increase in mortality.[2] Established nuclear medicine procedure wait times aim to optimize patient care and suggest that MPI should be performed within 24 hours for an emergency case (immediate danger to life, required for therapeutic management) and within three days for urgent cases (situation is unstable and has the potential to deteriorate quickly and result in an emergency admission).[14,15] Imaging results have moderate impact on patient management.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	The ACC/AHA guidelines for the management of patients with NSTEMI estimate the annual mortality rate to be between 1% (low risk) and 3% (high risk).[11] Improper risk stratification, as a result of not performing a diagnostic imaging test, could result in inappropriate treatment and could increase patient's risk of mortality. Diagnostic imaging test results can have a moderate impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Imaging allows for the identification of patients at risk of having a repeat MI and their appropriate treatment planning. Patients receiving treatment may be less likely to have a repeat MI. QoL scores are higher for MI patients if they believe they have control over their illness and treatment.[16] Some patients who did not undergo risk assessment may develop symptoms associated with MI including angina and shortness of breath (MIIMAC expert opinion). These symptoms may be associated with some morbidity and lower QoL. Diagnostic imaging test results can have a moderate impact on morbidity and quality of life.

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Indications		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally. There may be a disparity associated with how women are diagnosed, but this may be due in part to the fact that women are slower to present themselves to an emergency room compared to men.[17]
6	**Relative acceptability of the test to patients**	A 2004 British study compared patient satisfaction and preference toward SPECT versus MRI adenosine stress myocardial perfusion scans and found little difference.[18] The only statistically significant finding was that the SPECT scan was preferred in terms of space on the scanner.[18] Three participants (9%) stated that they would not have an MRI again, while two patients (6%) said they would not repeat a SPECT.[18] The study authors recognized that the relatively small sample size may have affected their ability to demonstrate statistically significant preference for one scan over the other.[18] Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. Patients undergoing CTCA may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. Echo may be preferred by some patients, as there is no radiation exposure with it. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[19,20] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. PET patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. SPECT stress MPI with ^{99m}Tc-labelled radiotracers: • is minimally less acceptable than CTCA • is minimally less acceptable than stress Echo • has similar acceptability as stress MRI

Table 1: Summary of Criterion Evidence

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Indications

Criterion		Synthesized Information
		• is minimally less acceptable than stress PET • has similar acceptability as stress SPECT with ^{201}TI-labelled radiotracers.
7	**Relative diagnostic accuracy of the test**	Two studies evaluated the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus its comparators in the assessment of prognosis post-MI: one compared ^{99m}Tc-labelled radiotracer SPECT with echo and MRI[7] and one compared ^{99m}Tc-labelled radiotracer SPECT with MRI.[8] Given the limited evidence regarding the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus its comparators in the assessment of prognosis post-MI, one study evaluating the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus PET was included.

Diagnostic Accuracy: Assessment of Prognosis Post-MI

Author, Date	N	Gold Standard	Intervention	Sensitivity (%)	Specificity (%)	Accuracy (%)
Lombardo, 2006[7]	14	^{99m}Tc-sestamibi SPECT	Echo	83	73	77
			MRI	65	78	73
Ibrahim, 2006[8]	78	Coronary angiography	MRI	97-100	NR	NR
			^{99m}Tc-sestamibi SPECT	79-89	NR	NR
Bateman, 2006[9]	224 (112 PET and 112 SPECT)	Clinical coronary angiogram reports	^{82}Rb-PET	87	93	89
			^{99m}Tc-sestamibi SPECT	82	73	79

Echo = echocardiogram; MRI = magnetic resonance imaging; n = size of a sub-sample; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technetium-99m.

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Indications		
Criterion		**Synthesized Information**
		Based on the available evidence, the diagnostic accuracy of ^{99m}Tc-SPECT is: • minimally better than stress CTCA • similar to stress Echo • minimally lower than stress MRI • minimally lower than stress PET • minimally better than ^{201}TI-SPECT stress imaging.
8	**Relative risks associated with the test**	**Non–radiation-related risks** The main risks of non-invasive preoperative assessment relate to the stress component of the tests. With exercise stress testing, there is a small risk of the patient sustaining an MI if they have significant coronary artery disease.[21] With dipyridamole stress testing, there are multiple potential side effects, including headache, exacerbated asthma, and heart attack (risk of this event is low).[21] With adenosine stress testing, side effects similar to dipyridamole may be experienced. Symptoms of chest pain or pressure may also occur, but these side effects disappear quickly once the adenosine administration stops.[21] With dobutamine stress testing, some patients may experience light-headedness and nausea. There is a theoretical risk of inducing a fast and abnormal cardiac rhythm (i.e., atrial fibrillation, ventricular tachycardia, ventricular fibrillation); however, this is unlikely with the doses of dobutamine used. The overall risk of sustaining a heart attack from a stress test is estimated to be about 2 to 4 in 10,000.[21] Apart from risks associated with stress testing, the radiopharmaceuticals used in SPECT imaging may cause reactions in some patients. These reactions are rare and include skin and anaphylactic reactions.[22] With CTCA, some patients may experience mild, moderate, or severe side effects from the contrast agent. The frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions is also rare (0.004% to 0.7%).[23] Apart from risks associated with stress testing, there is a low risk of adverse events associated with the contrast used in stress Echo imaging. Apart from risks associated with stress testing, some patients may experience a reaction to the contrast agent Gd used in MRI. Reactions may include headaches, nausea, and metallic taste. The frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions is also rare (0.004% to 0.7%)[23]

Table 1: Summary of Criterion Evidence

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Indications

Criterion	Synthesized Information

Apart from risks associated with stress testing, the Pharmacopeia Committee of the SNM conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[24] The risks associated with stress testing would apply for cardiac imaging using PET.

Radiation-related Risks

Among the modalities to diagnose ischemia, SPECT MPI, CTCA, and stress PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in the following table.

Effective Doses of Radiation

Procedure	Average Effective Dose (mSv)
^{99m}Tc-SPECT MPI	7 to 12.8[25]
^{201}Tl-SPECT MPI	17 to 41[25,26]
Cardiac ^{18}FDG-PET	7 to 14 (MIIMAC expert opinion)[26]
Cardiac ^{82}Rb-PET	1.1 to 5.0[26-28]
Cardiac $^{13}NH_3$-PET	1.5 to 2.2[28]
CTCA	2.1 to 16[29,30]
MRI	0
Echo	0
Average background dose of radiation per year	1-3.0[31-33]

CTCA = computed tomography coronary angiography; Echo = echocardiogram; ^{18}FDG = fluorodeoxyglucose; MPI = myocardial perfusion imaging; mSv = millisievert; $^{13}NH_3$ = 13N-labelled ammonia; PET = positron computed tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technetium-99m; ^{201}Tl = thallium-201.

Overall, ^{99m}Tc-SPECT MPI:

- and CTCA have similar safety profiles
- and stress Echo have similar safety profiles
- and stress MRI have similar safety profiles
- and stress PET have similar safety profiles
- and ^{201}TI-SPECT have similar safety profiles.

Table 1: Summary of Criterion Evidence		
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Indications		
Criterion		**Synthesized Information**
9	**Relative availability of personnel with expertise and experience required for the test**	In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic nuclear imaging, CT scans, MRI, and U/S should be diagnostic radiologists or nuclear medical physicians. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). Not all radiologists, nuclear medical physicians, nuclear cardiologists, or cardiologists have the expertise to conduct ^{99m}Tc-SPECT and all of its alternatives. For example, a 2002 report by the Canadian Cardiovascular Society reported that 43% of cardiologists do Echo. Assuming the necessary equipment is available, if ^{99m}Tc-SPECT imaging is not available, it is estimated that: • 25% to 74% of the procedures can be performed in a timely manner using CTCA • 25% to 74% of the procedures can be performed in a timely manner using Echo • fewer than 25% of the procedures can be performed in a timely manner using MRI • 25% to 74% of the procedures can be performed in a timely manner using PET • more than 95% of the procedures can be performed in a timely manner using ^{201}TI-SPECT.
10	**Accessibility of alternative tests (equipment and wait times)**	For SPECT MPI, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of 2007, no nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[34] No CT scanners are available in Nunavut.[35] For CT scanners, the average weekly use ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[34] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[36] The average wait time for a CTCA was not reported. Of note, not all CT scanners are capable of performing cardiac CT. No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[35] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[34] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[36] A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[37] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[37] There are a total of 36 PET or PET/CT scanners in Canada, four of which are used for research purposes only.[37]

Table 1: Summary of Criterion Evidence

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Indications

Criterion		Synthesized Information
		U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[36] • 25% to 74% of the procedures can be performed in a timely manner using CTCA • 75% to 94% of the procedures can be performed in a timely manner using Echo • fewer than 25% of the procedures can be performed in a timely manner using MRI • fewer than 25% of the procedures can be performed in a timely manner using PET • more than 95% of the procedures can be performed in a timely manner using ^{201}TI-SPECT.
11	**Relative cost of the test**	According to our estimates, the cost of myocardial perfusion imaging with ^{99m}Tc-based radioisotopes is $964.53. The cost of myocardial perfusion imaging with ^{201}TI or with PET is assumed to be greater than imaging with ^{99m}Tc-based radioisotopes. Stress MRI is minimally less costly than myocardial perfusion imaging with ^{99m}Tc. CTCA and stress echo are moderately less costly.

Relative costs

Test	Total costs ($)	Cost of test relative to ^{99m}Tc-based test ($)
^{99m}Tc-SPECT MPI	964.53	Reference
^{201}TI-SPECT MPI	964.53	+0.00
CTCA	506.03	-458.50
Stress Echo	466.90	-497.63
Stress MRI	835.16	-129.37
Stress PET	1128.60	+164.07

ACC = American College of Cardiology; AHA = American Heart Association; AMI = acute myocardial infarction; CIHI = Canadian Institute for Health Information; CMA = Canadian Medical Association; CT = computed tomography; CTCA = computed tomography coronary angiography; Echo = stress echocardiography; ^{18}FDG = ^{18}F-fluorodeoxglucose; Gd = gadolinium; MI = myocardial infarction; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; mSv = millisievert; NSTEMI = non-ST elevation myocardial infarction; PET = positron emission tomography; Prof = professional; QoL = quality of life; SNM = Society of Nuclear Medicine; SPECT = single-photon emission computed tomography; Tech = technical; ^{82}Rb = rubidium-82; ^{99m}Tc = Technetium-99m; ^{201}Tl = thallium-201; U/S = ultrasound.

CRITERION 1: Size of affected population (link to definition)

In 2009, the Public Health Agency of Canada (PHAC) published a report on heart disease and stroke in Canada.[12] According to this report, there were 60,996 hospitalizations due to heart attacks in the 2006-2007 fiscal year (crude rate: 188.2 per 100,000 people).[12] The authors of the report noted that the age-standardized rate of hospitalization due to heart attack has decreased from 1971 to 2007, likely due to better prevention and management of ischemic heart disease.[12]

A 2010 publication by Statistics Canada and the Canadian Institute for Health Information (CIHI) reported that 66,707 Canadians were hospitalized for a heart attack in the 2008-2009 fiscal year and provided an age-standardized hospitalization rate of 217/100,000 adults (20 years of age or older).[13] This report also noted that 2,266 Canadians (3.4% of heart attack victims) had more than one heart attack in a year.[13]

MI rates vary across the country; however, the rate is lowest in Nunuvat: 112/100,000 (range: 49 to 176) and highest in Newfoundland and Labrador 347/100,000 (range 330 to 363).[13]

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

A delay in the revascularization process may result in irreversible damage to the myocardium and is associated with an increase in mortality.[2] Established nuclear medicine procedure wait times aim to optimize patient care and suggest that MPI should be performed within 24 hours for an emergency case (immediate danger to life, required for therapeutic management) and within three days for urgent cases (situation is unstable and has the potential to deteriorate quickly and result in an emergency admission).[14,15]

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

The goals of non-invasive stress testing are to:

- determine the presence or absence of ischemia
- estimate patient prognosis.[11]

Therefore, the impact of not performing a diagnostic imaging test could include misdiagnosis of ischemia or improper risk stratification.

Misdiagnosis of ischemia

A study published in 2000[38] investigated the incidence misdiagnosis of acute cardiac ischemia (i.e., either acute myocardial infarction or unstable angina) in ten United States hospitals. The hospitals included a mix of public, private, community, and tertiary care hospitals with urban, suburban, and semi-rural catchment areas in the Midwestern, Southeastern, and Northeastern United States.[38] The rate of missed diagnoses of MI among non-hospitalized cases was 2.1% (19 of 889).[38] Importantly, the risk-adjusted ratio of observed to predicted mortality showed that non-hospitalized patients with an MI had a risk of death that was 1.9 (95% confidence interval [CI], 0.7 to 5.2) times that of the patients who were hospitalized.

Improper risk stratification
The American College of Cardiology/American Heart Association (ACC/AHA) guidelines for the management of patients with NSTEMI include a table of non-invasive criteria for estimating patient risk of mortality (Appendix 3).[11] According to these criteria, the annual mortality rate varies from 1% (low risk) to greater than 3% (high risk).[11] Improper risk stratification, as a result of not performing a diagnostic imaging test, could result in improper treatment and could increase a patient's risk of mortality.

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

A meta-analysis published in 2007 of 17 MPI studies including 8,008 subjects (mean age 54 years) reported the risk of an MI after a normal MPI test was 1.2%.[39]

The estimated prevalence of the Ontario population in 2004 that survived a previous MI hospital admission is 2.03% (95% CI, 2.01 to 2.05) or approximately 170,000 people.[40]

There were five studies identified (1999 to 2010)[16,41-44] that measured the quality of life (QoL) of patients with an MI using the Medical Outcomes Study Short-Form 36 (SF-36),[45] which is a generic QoL instrument. The SF-36 instrument contains eight domains: physical function (PF), role-physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), role-emotional (RE), mental health (MH); and two summary scores — physical component score (PCS) and mental component score (MCS). Scores are all standardized and range from zero to 100, with higher scores indicating better QoL.

Brown et al.[43] sent questionnaires to a cohort of 495 patients from the Nottingham Heart Attack Register who had an MI in 1992 and were still alive four years later. The SF-36 scores were compared with two population norms: Oxford norms for patients under the age of 65 and Sheffield norms for patients over 65. Statistically significantly lower scores for all eight domains were reported by MI survivors less than 65 years of age. There were no differences in the Nottingham patient scores and the Sheffield normative scores for patients greater than 65 years of age, suggesting that QoL scores of patients of retirement age or older are similar to four-year MI survivors. Similar results are reported by a recent 2010 report by Alsén et al.[16] who followed 204 Swedish MI patients, except that bodily pain was not different between the MI patients and the normative group.

Brink et al.[42] followed a cohort of Swedish MI patients — 33 women (mean age [standard deviation (SD)]: 64.6 years [9.8 years] and 65 men (mean age [SD]: 71.4 years [8.7years]). The authors reported improved SF-36 scores at one year compared to five months post-MI, with the changes reaching statistical significance for the VT, RE, and MH domains, as well as the MCS score. The BP score for the MI group was the only domain score that reached the level of the normative score. In comparison with normative scores, women scored statistically significantly lower on four domains (PF, RP, SF, RE), whereas men reported statistically significantly lower scores on three domains (PF, RP, VT).

Failde and Soto[44] measured QoL using the SF-36 at three months post-MI in 76 Spanish patients, of which 78.5% were > 55 years of age. The authors reported statistically significantly lower scores in the PF, GH, VT, and PCS scores. The other domain scores were not different. This is similar to a 2001 Canadian study,[41] where 587 patients were enrolled in a QoL-after-MI

study. The mean age (SD) of the patients was 61 years (1.2 years). The authors reported that PCS and MCS scores were slightly lower than the baseline scores and they did not change throughout the one-year follow-up.

An inability to return to work or be fit for work, chest pain on a weekly basis, use of inhalers, anxiolytic/hypnotics, and antiarrhythmics were all associated with lower QoL scores.[43] The more patients believed their illness to be chronic and episodic in nature, and the more they believed that the condition would have consequences in their lives, the lower the PSC and MCS scores.[16] Higher PCS scores were seen when the patients believed they had more personal and treatment control over their illness.[16] Age and previous bypass surgery are predictors of impaired PSC scores.[41] Having a subsequent MI after discharge is associated with a statistically significantly increased risk for decline in physical functioning (odds ratio [OR]=2.64; 95% CI, 1.45 to 4.82, $P < 0.001$).[46]

Return to Summary Table.

CRITERION 5: Relative impact on health disparities (link to definition)

In a population-based study of patients hospitalized for an MI from four American centres, published in 2008,[47] it was reported that women with no history of MI were less likely to undergo angiography (OR 0.72 [95% CI, 0.57 to 0.89]) or Echo (OR 1.58 [95% CI, 1.32 to 1.90]). In the two sites where there was a large number of patients of black race, they reported that black people were more likely to undergo an Echo (OR 1.89 [CI, 1.62 to 2.19]) or have nuclear testing (OR 1.63 [95% CI, 1.27 to 2.09]) compared to Caucasian patients.

From a German registry, female patients with an acute ST-elevation MI had a pre-hospital delay of 195 minutes, and fewer women presented to the emergency room during the first hour following the onset of symptoms.[17]

Return to Summary Table.

CRITERION 6: Relative acceptability of the test to patients (link to definition)

SPECT
A 2004 British study compared patient satisfaction and preference toward SPECT versus MRI adenosine stress myocardial perfusion scans and found little difference.[18] Forty-one patients who had undergone both SPECT and MRI were sent a retrospective questionnaire within two weeks of scan completion. Thirty-five completed questionnaires were returned. When asked, “If the two tests (nuclear heart scan and MRI) could provide the same information, which of the two would you prefer?”, 12 patients (34%) stated a preference for MRI, nine (26%) stated a preference for SPECT, and 14 (40%) stated no preference.[18] Patients rated the two tests similarly on overall preference, duration, comfort, and safety, with a non-significant preference for MRI on all of the above mentioned.[18] The only statistically significant finding was that the SPECT scan was preferred in terms of space on the scanner.[18] Three participants (9%) stated that they would not have an MRI again, while two patients (6%) said they would not repeat a SPECT.[18] Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. The study authors recognized that the relatively small sample size may have affected their ability to demonstrate statistically significant preference for one scan over the other.[18]

CTCA
Patients undergoing computed tomography coronary angiography scans may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion).

Stress Echo
This test is likely to be well-tolerated by patients. Echo may be preferred by some patients, as there is no radiation exposure. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Stress MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension, and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[19,20] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Stress PET MPI (^{82}Rb or 13N-labelled ammonia [$^{13}NH_3$])
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Return to Summary Table.

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Two studies identified in the primary literature search evaluated the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus its comparators in the assessment of prognosis post-MI: one comparing ^{99m}Tc-labelled radiotracer SPECT with Echo and MRI[7] and one comparing ^{99m}Tc-labelled radiotracer SPECT with MRI.[8] No studies comparing ^{99m}Tc-labelled radiotracer SPECT with CT, PET, or ^{201}TI-labelled radiotracer SPECT met the inclusion criteria.

MRI and myocardial contrast echo (MCE) versus ^{99m}Tc-labelled radiotracer SPECT
Lombardo et al.[7] evaluated the accuracy of MCE and MRI in identifying myocardial perfusion defects in AMI patients, using ^{99m}Tc-labelled radiotracer SPECT as the reference standard. The study population consisted of 14 patients admitted with a diagnosis of first acute MI.[7] MCE, MRI, and ^{99m}Tc-labelled radiotracer SPECT studies were performed within five days of hospital admission, while standard coronary angiography was conducted within the initial seven days.[7] Five patients underwent percutaneous coronary intervention (PCI) and five were treated with thrombolytic therapy.[7] Only 153 of 224 segments (68%) imaged with Echo and 220 of 224 segments (98%) imaged by MRI were suitable for interpretation and analysis. Echo showed a statistically significantly higher sensitivity than MRI, when compared with ^{99m}Tc-labelled radiotracer SPECT (Table 2).

Table 2: Diagnostic Accuracy of Echo and MRI with ^{99m}Tc-labelled Radiotracer SPECT as the Reference Standard		
Criterion	**Echo**	**MRI**
Sensitivity (%)	83	65
Specificity (%)	73	78
Accuracy (%)	77	73

Echo = echocardiography; MRI = magnetic resonance imaging SPECT = single-photon emission computer tomography; ^{99m}Tc = Technetium-99m.

MRI versus ^{99m}Tc-labelled radiotracer SPECT

Ibrahim et al.[8] investigated the diagnostic value of contrast-enhanced MRI and ^{99m}Tc-labelled radiotracer SPECT for the detection of myocardial necrosis in patients early on following an AMI and reperfusion therapy. Seventy-eight patients with a diagnosis of AMI (based on chest pain lasting a minimum of 20 minutes and associated with electrocardiographic changes and elevated troponin T activity) were included in the analysis. MRI and ^{99m}Tc-labelled radiotracer SPECT tests were performed in all patients a median of seven days post-MI.[8] MRI and ^{99m}Tc-labelled radiotracer SPECT images were analyzed using a 17-segment model, with semi-quantitative scoring. Sensitivity of MRI and SPECT was determined for the detection of myocardial necrosis. The sensitivity of MRI was shown to be higher in all vascular areas, although the difference was not statistically significant (Table 3).[8]

Table 3: Sensitivity of MRI and ^{99m}Tc-labelled Radiotracer SPECT for Detection of Myocardial Necrosis[8]		
Infarct-Related Artery	**^{99m}Tc-labelled Radiotracer SPECT**	**MRI**
Left anterior descending artery (%)	89	97
Left circumflex artery (%)	79	100
Right coronary artery (%)	87	97

MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99.

Given the limited evidence regarding the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus its comparators in the assessment of prognosis post-MI, studies evaluating the diagnostic accuracy of ^{99m}Tc-labelled radiotracer SPECT versus its comparators in the diagnosis of ischemia are subsequently included.

^{82}Rb-PET versus ^{99m}Tc-labelled radiotracer SPECT

Bateman et al.[9] compared the diagnostic accuracy of ^{99m}Tc-sestamibi SPECT and ^{82}Rb-PET for MPI of patients matched by gender, body mass index, and presence and extent of coronary disease. Included patients were identified retrospectively from an electronic nuclear cardiology database and were categorized as having a low likelihood for coronary artery disease (n = 54) or had coronary angiography within 60 days (n = 170).[9] Twenty-four of the 112 patients (21%) who underwent SPECT and 28 of the 112 patients (25%) who underwent PET had had a previous MI.[9] Four experienced nuclear medicine cardiologists blinded to patients' clinical information interpreted scans obtained from 112 ^{99m}Tc-labelled radiotracer SPECT and 112 ^{82}Rb-PET electrocardiogram-gated rest/pharmacologic stress studies.[9] By consensus, the quality of the perfusion images were deemed superior with PET (78% and 79% for rest and stress scans, respectively) than SPECT (62% and 62%; both $P > 0.05$).[9] Interpretive certainty was also rated higher with PET versus SPECT scans (96% versus 81%, $P = 0.001$). Diagnostic accuracy was better for PET over SPECT. For patients with a stenosis severity of 70% by angiography, the sensitivity was 82% for SPECT and 87% for PET ($P = 0.41$), and the specificity was 73% for SPECT versus 93% for PET ($P = 0.02$), resulting in a significant improvement in overall accuracy by PET (89% versus 79%, $P = 0.03$) (Table 4).[9] Bateman and colleagues conclude that, for this patient population, a major benefit of PET versus SPECT is higher diagnostic accuracy.[9]

Table 4: Diagnostic Characteristics of ^{18}FDG-PET and ^{99m}Tc-labelled Radiotracer SPECT (70% stenosis as CAD)		
	^{99m}Tc-labelled radiotracer SPECT	**^{82}RB-PET**
Sensitivity (%)	82	87
Specificity (%)	73	93
Accuracy (%)	79	89

CAD = coronary artery disease; ^{18}FDG-PET = fluorodeoxyglucose -18 positron emission tomography; ^{82}RB-PET = rubidium-82 positron emission tomography; SPECT = single-photon emission computer tomography; ^{99m}Tc = technetium-99.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related risks

Cardiac stress tests

The main risks of non-invasive preoperative assessment relate to the stress component of the tests:

- With exercise stress testing, there is a small risk of the patient sustaining an MI if they have significant coronary artery disease.[21]
- With dipyridamole stress testing, there are multiple potential side effects, including headache, exacerbated asthma, and heart attack (risk of this event is low).[21]
- With adenosine stress testing, side effects similar to dipyridamole may be experienced. Symptoms of chest pain or pressure may also occur, but these side effects go away quickly once the adenosine administration stops.[21]
- With dobutamine stress testing, some patients may experience light-headedness and nausea. There is a theoretical risk of inducing a fast and abnormal cardiac rhythm (i.e., atrial fibrillation, ventricular tachycardia, ventricular fibrillation); however, this is unlikely with the doses of dobutamine used. A slight risk of MI exists.[21]

The overall risk of sustaining a heart attack from a stress test is estimated to be about two to four per 10,000 tests.[21]

Stress SPECT

Apart from risks associated with stress testing, a review of undesirable events with radiopharmaceuticals reported anaphylactic reactions and erythema multiforme (i.e., a type of skin reaction) with sestamibi, although these reactions may be rare.[22]

CTCA

Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[48] In addition, patients may experience mild side effects from the contrast agent such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium (Gd) contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[49] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. Patients must be able to take rate-lowering medications. Although rarely used in cardiac imaging, Gd is contraindicated in patients with renal failure or end-stage renal disease, as these patients are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology Manual on Contrast Media,[23] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%).

Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[23]

Stress Echo
Apart from risks associated with stress testing, three relatively large studies with sample sizes of 42,408 patients (2009),[50] 26,774 patients (2009),[51] and 5,069 patients (2008)[52] compared cardiac outcomes (non-fatal MI or death) between patients who underwent contrast-enhanced Echo with patients who had an Echo without contrast. All three studies concluded that the risk of an adverse event is low and is no different than that of patients who received no contrast. No additional risks associated with Echo were identified.

Stress MRI
Apart from risks associated with stress testing, MRI is contraindicated in patients with metallic implants including pacemakers.[53] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[48] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology Manual on Contrast Media,[23] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[23]

Stress PET
The Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[24] The risks associated with stress testing would apply for cardiac imaging using PET.

Radiation-related Risks

Among the modalities to diagnose ischemia, SPECT MPI, CTCA, and stress PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 5.

Table 5: Effective Doses of Radiation

Procedure	Average Effective Dose (mSv)
^{99m}Tc-SPECT MPI	7 to 12.8[25]
^{201}Tl-SPECT MPI	17 to 41[25,26]
Cardiac ^{18}FDG-PET	7 to 14 (MIIMAC expert opinion)[26]
Cardiac ^{82}Rb-PET	1.1 to 5.0[26-28]
Cardiac $^{13}NH_3$-PET	1.5 to 2.2[28]
CTCA	2.1 to 16[29,30]
MRI	0
Echo	0
Average background dose of radiation per year	1-3.0[31-33]

CTCA = computed tomography coronary angiography; Echo = echocardiography; ^{18}FDG = fluorodeoxyglucose -18; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; mSv = millisevert; $^{13}NH_3$ = 13N-labelled ammonia; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission tomography; ^{99m}Tc = technetium-99; ^{201}Tl = thallium-201.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to assess patient prognosis post-MI are presented by imaging modality. A summary of the availability of personnel required for the conduct of post-myocardial infarction assessment of prognosis, by SPECT or any of the alternative imaging modalities, is provided in Table 6.

^{99m}Tc-labelled radiotracer SPECT MPI

In Canada, physicians involved in the performance, supervision, and interpretation of cardiac nuclear imaging (specifically MPI using ^{99m}Tc-labelled radiotracer) should be nuclear medicine physicians with particular expertise in nuclear cardiology (nuclear cardiologists). Cardiologists also provide nuclear cardiology services. According to the Canadian Medical Association (CMA), there are 1,149 practicing cardiologists in Canada (CMA, 2011).

Nuclear medicine technologists are required to conduct MPI. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

All alternative imaging modalities

In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound (U/S) should be diagnostic radiologists[34] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists are also qualified if they are certified by a recognized certifying body and hold a valid provincial license.[54] According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011).

Medical radiation technologists (MRTs) must be certified by CAMRT, or an equivalent licensing body. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Service engineers are needed at regularly scheduled intervals for system installation, calibration, and preventive maintenance of the imaging equipment. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (onsite or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[54]

CTCA

CTCA is a CT-based test. Cardiologists provide much of the CTCA service. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011).

For the performance of a CT scan, medical radiation technologists certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

Stress Echo
Echocardiography is a U/S-based test. Cardiologists provide much of the Echo service. A 2002 report by the Canadian Cardiovascular Society (CCS) reported that 43% of cardiologists do echocardiography. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). It is assumed that less than 500 of them do echocardiography.

Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals (CARDUP). They should be members of their national or provincial professional organizations. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[34] In Quebec, sonographers and MRTs are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[34] A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Stress MRI
Medical technologists must have CAMRT certification in MRI or be certified by an equivalent licensing body recognized by CAMRT. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Stress PET
In Canada, physicians involved in stress PET scanning should be nuclear medicine physicians, nuclear cardiologists, or cardiologists with training and expertise in nuclear imaging. In Canada, physicians who perform PET imaging studies must be certified by either the Royal College of Physicians and Surgeons of Canada or le Collège des médecins du Quebec.

Technologists must be certified by CAMRT or an equivalent licensing body. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Table 6: Medical Imaging Professionals in Canada, 2006[34]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**MRTs**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRT = medical radiation technologist; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

Expertise

Two studies determined the intra- and inter-observer variability of ^{99m}Tc-labelled radiotracer SPECT, Echo, and MRI images. An Italian study[55] evaluated scans from 56 patients (mean age [SD]: 52 years [9 years]) who had an MI and the second study[56] evaluated 42 patient scans (mean age [SD]: 59 years [19 years]). The kappa scores for inter- and intra-rater agreement are listed in Table 7.

Table 7: Kappa Scores				
Study		**^{99m}Tc-labelled Radiotracer SPECT**	**Echo**	**MRI**
Ferro[55]	Inter-rater Intra-rater	0.92 0.96	0.56 0.81	NA NA
Janardhanan[56]	Inter-rater Intra-rater	NA NA	0.76 0.77	0.66 0.72

Echo = echocardiography; MRI = magnetic resonance imaging; NA=not applicable; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99.

Based on the data provided in Table 7, ^{99m}Tc-labelled radiotracer SPECT has a better interpretive reproducibility than Echo or MRI.

Others have reported intra-observer variability between two experienced readers evaluating contrast-enhanced Echo images of 4 ± 2% and 1 ± 1% for MRI. The inter-observer variability (images read 15 days later) was reported as 8 ± 3% for contrast-enhanced Echo and 3 ± 1% for MRI .[7]

Cardiac measures using Echo scans are the least reproducible compared with SPECT and MRI scans.

A report from the United States[57] states that employment of cardiovascular technologists and technicians is expected to increase 24% through the year 2018 — much faster than the average for other occupations. Demand will stem from the prevalence of heart disease and the aging population, because older people have a higher incidence of heart disease and other complications of the heart and vascular system.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 8 provides an overview of the availability of equipment required to detect ischemia. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010. Data were not available for Echo.

Table 8: Diagnostic Imaging Equipment in Canada[34,35,37]

	Nuclear Medicine Cameras	CT Scanners	MRI Scanners	PET or PET/CT
Number of devices	603[34]	460[35]	218[35]	36[37]
Average number of hours of operation per week (2006-2007)	40	60	71	NA
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	NL, PEI, SK, YT, NT, NU

CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; NB = New Brunswick; NL. = Newfoundland; NS = Nova Scotia; NU = Nunavut; NT = Northwest Territories; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon.

^{99m}Tc-labelled radiotracer SPECT

Nuclear medicine facilities with gamma cameras are required for SPECT imaging. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[34]

CT

No CT scanners are available in Nunavut.[35] The average weekly use of CT scanners ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[34] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[36] The average wait time for CTCA was not reported.

Echo

No information was found to identify how many Echo machines are available in Canada.

MRI

No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[35] According to the Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[34] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[36]

PET
A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[37] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[37] There are 36 PET or PET/CT scanners in Canada, four of which are used for research purposes only.[37]

Wait times
Wait time benchmarks for cardiac nuclear imaging set by the Wait Time Alliance[14] are immediate to 24 hours for emergency cases (immediate danger to life, limb, or organ); within three days for urgent cases (situation that is unstable and has the potential to deteriorate quickly and result in an emergency admission); and within 14 days for scheduled cases (situation involving minimal pain, dysfunction, or disability — routine or elective).

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of SPECT MPI and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP; estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 9), the cost of myocardial perfusion imaging with ^{99m}Tc-based radioisotopes is $964.53. The cost of myocardial perfusion imaging with ^{201}TI or with PET is assumed to be greater than imaging with ^{99m}Tc-based radioisotopes. Stress MRI is minimally less costly than myocardial perfusion imaging with ^{99m}Tc. CTCA and stress echo are moderately less costly.

Table 9: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[58]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
	^{99m}Tc-SPECT MPI			
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)	44.60	31.10	75.7
J813	Studies with ejection fraction	138.60	82.25	220.85
J807	Myocardial perfusion scintigraphy — resting, immediate post-stress	223.15	50.15	273.3
J808	Myocardial perfusion imaging — delayed	82.15	27.45	109.6
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole Thallium stress test	52.05	75.00	127.05

Maintenance fees — from global budget		50.78		50.78
	TOTAL	635.93	328.6	**964.53**
^{201}TI-SPECT MPI				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)	44.60	31.10	75.7
J813	Studies with ejection fraction	138.60	82.25	220.85
J807	Myocardial perfusion scintigraphy — resting, immediate post stress	223.15	50.15	273.3
J808	Myocardial perfusion imaging — delayed	82.15	27.45	109.6
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole Thallium stress test	52.05	75.00	127.05
Maintenance fees — from global budget		50.78		50.78
	TOTAL	635.93	328.6	**964.53**
CTCA				
X235	Cardiothoracic CT		155.25	155.25
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		50.78		50.78
	TOTAL	350.78	155.25	**506.03**
Stress echo				
G570/G571	Complete study — 1 and 2 dimensions	76.45	74.10	150.55
G577/G578	Cardiac Doppler study, with or without colour Doppler, in conjunction with complete 1 and 2 dimension echocardiography studies	45.15	36.90	82.05
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole Thallium stress test	52.05	75.00	127.05
	TOTAL	218.25	248.65	**466.90**
Stress MRI				
X441C	MRI — thorax — multislice sequence		77.20	77.20
X445C (×3)	Repeat (another plane, different pulse sequence — to a maximum of 3 repeats)		38.65 (×3) = 115.95	115.95
X499C	3-Dimensional MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40
G315/G319	Maximal stress ECG	44.60	62.65	107.25
X486C	When cardiac gating is performed (must include application of chest electrodes and ECG interpretation), add 30%		96.36	96.36
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	417.60	417.56	**835.16**
Stress PET				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)		31.10	31.10
J813	Studies with ejection fraction		82.25	82.25
J807	Myocardial perfusion scintigraphy — resting, immediate post-stress		50.15	50.15
J808	Myocardial perfusion imaging — delayed		27.45	27.45

G315/G319	Maximal stress ECG		62.65	62.65
G111/G112	Dipyridamole Thallium stress test		75.00	75.00
Technical cost — from global budget		800.00		800.00
	TOTAL	800.00	328.60	**1128.60**

3-D = three-dimensional; CT = computed tomography; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; PET = positron emission tomography; Prof. = professional; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m; ^{201}TI = thallium-201; tech. = technical.

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Appendix 1: Multi-criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing Between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing Between Clinical Uses	
Criterion	**Definition**
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to February 24, 2011>
Date of Search:	February 24, 2011
Alerts:	Monthly search updates began February 24, 2011 and ran until October 2011.
Study Types:	Health technology assessments; systematic reviews; meta-analyses; randomized controlled trials; controlled clinical trials; diagnostic accuracy studies
Limits:	English language Publication years 2006-February 2011 for primary studies search; no date limits for systematic review search. Primary studies search limited to human population

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search; includes title, abstract, name of substance word, subject heading word, and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use

Multi-Database Strategy	
#	**Searches**
1	exp Myocardial Infarction/
2	((myocardial or postmyocardial or myocardium or heart or cardiac) adj (infarction or infarctions or infarct or infarcts or infarcted or attack or attacks)).ti,ab.
3	1 or 2
4	Technetium/
5	exp Technetium Compounds/
6	exp Organotechnetium Compounds/
7	exp Radiopharmaceuticals/
8	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.

Multi-Database Strategy	
9	Radionuclide Imaging/ or Perfusion Imaging/
10	radionuclide imaging.fs.
11	radioisotope*.mp.
12	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
13	Exp Tomography, Emission-Computed, Single-Photon/
14	(single-photon adj2 emission*).ti,ab.
15	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
16	Myocardial Perfusion Imaging/
17	(myocardial perfusion imag* or MPI or rMPI or rest-stress test* or cardiac-stress test*).ti,ab.
18	(sestamibi or Hexamibi or Tc MIBI or Cardiolite* or tetrofosmin* or myoview*).ti,ab.
19	(109581-73-9 or 112144-90-8 or 113720-90-4).rn.
20	or/4-19
21	meta-analysis.pt.
22	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
23	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
24	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
25	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
26	(data synthes* or data extraction* or data abstraction*).ti,ab.
27	(handsearch* or hand search*).ti,ab.
28	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
29	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
30	(meta regression* or metaregression* or mega regression*).ti,ab.
31	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
32	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
33	(cochrane or health technology assessment or evidence report).jw.
34	or/21-33
35	exp "Sensitivity and Specificity"/
36	False Positive Reactions/
37	False Negative Reactions/
38	sensitivit*.ti.
39	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti.
40	(predictive adj4 value*).ti,ab.
41	Validation Studies.pt.
42	or/35-41
43	(Randomized Controlled Trial or Controlled Clinical Trial).pt.
44	Randomized Controlled Trial/
45	Randomized Controlled Trials as Topic/
46	Controlled Clinical Trial/
47	Controlled Clinical Trials as Topic/
48	Randomization/

Multi-Database Strategy	
49	Random Allocation/
50	Double-Blind Method/
51	Double-Blind Studies/
52	Single-Blind Method/
53	Single-Blind Studies/
54	Placebos/
55	Control Groups/
56	Control Group/
57	(random* or sham or placebo*).ti,ab,hw.
58	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
59	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
60	(control* adj3 (study or studies or trial*)).ti,ab.
61	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
62	allocated.ti,ab,hw.
63	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
64	or/43-63
65	3 and 20 and 34
66	65
67	limit 66 to english language
68	3 and 20 and 42
69	3 and 20 and 64
70	68 or 69
71	exp animals/
72	exp animal experimentation/
73	exp models animal/
74	exp animal experiment/
75	nonhuman/
76	exp vertebrate/
77	or/71-76
78	exp humans/
79	exp human experiment/
80	or/78-79
81	77 not 80
82	70 not 81
83	82 not case reports.pt.
84	83
85	limit 84 to (english language and yr="2006 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
The Cochrane Library (Issue 1, 2011)	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and human restrictions. Syntax adjusted for The Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	February 25 to March 1, 2011
Keywords:	Included terms for myocardial infarction and radionuclide imaging
Limits:	English language

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Non-invasive Criteria for Establishing Risk from the American College of Cardiology/American Heart Association/ Guidelines for the Management of Patients with Unstable Angina/ Non–ST-Segment Elevation Myocardial Infarction[11]

High risk (greater than 3% annual mortality rate)

- Severe resting left ventricular (LV) dysfunction (left ventricular ejection fraction [LVEF] less than 0.35)
- High-risk treadmill score (score -11 or less)
- Severe exercise LV dysfunction (exercise LVEF < 0.35)
- Stress-induced large perfusion defect (particularly if anterior)
- Stress-induced multiple perfusion defects of moderate size
- Large, fixed perfusion defect with LV dilation or increased lung uptake (thallium-201[^{201}Tl])
- Stress-induced moderate perfusion defect with LV dilation or increased lung uptake (^{201}Tl)
- Echocardiographic wall-motion abnormality (involving more than two segments) developing at low dose of dobutamine (10 mg per kg per minute or less) or at a low heart rate (less than 120 beats per minute)
- Stress echocardiographic evidence of extensive ischemia

Intermediate risk (1% to 3% annual mortality rate)

- Mild/moderate resting LV dysfunction (LVEF -0.35 to 0.49)
- Intermediate-risk treadmill score (-11 to 5)
- Stress-induced moderate perfusion defect without LV dilation or increased lung intake (^{201}Tl)
- Limited stress echocardiographic ischemia with a wall-motion abnormality only at higher doses of dobutamine involving less than or equal to two segments

Low risk (< 1% annual mortality rate)

- Low-risk treadmill score (score 5 or greater)
- Normal or small myocardial perfusion defect at rest or with stress
- Normal stress echocardiographic wall motion or no change of limited resting wall-motion abnormalities during stress

APPENDIX 2.8

INDICATION OVERVIEW

Ischemia results from the inadequate supply of blood to an organ or tissue caused by blockage of the blood vessels to the area. Within the heart, this blockage is most often due to coronary atherosclerosis-related stenosis (narrowings). Myocardial ischemia (lack of blood flow to the heart) is the most common cause of symptoms of coronary heart disease — also referred to as coronary artery disease (CAD).[1] Prolonged or significant ischemic conditions in the heart may result in a myocardial infarction (MI) — that is, a heart attack — or sudden death. MIs contribute to heart failure. Therefore, diagnosis of CAD prior to a heart attack or other event is important. Symptoms of myocardial ischemia may include chest pain, shortness of breath, nausea and vomiting, palpitations, and sweating. In some cases, myocardial ischemia is not associated with any symptoms (silent ischemia).

In addition to clinical symptoms and laboratory testing, cardiac imaging is often used in patients suspected to have CAD. Imaging can assist not only in detecting ischemia and diagnosing CAD, but also in stratifying patients according to their risk of having an ischemic event — low, intermediate, or high. Risk stratification can assist physicians in planning patient management. Imaging in patients with known CAD is also performed to assess the extent of damage to the myocardium, or heart tissue. Patients with viable myocardium may benefit from revascularization,[2] a treatment that involves restoring the flow of blood to damaged areas of the myocardium.

Population: Patients with suspected CAD (for diagnosis and immediate treatment) or patients with known CAD undergoing risk stratification and subsequent treatment planning.

Intervention: Stress single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) with technetium-99m (^{99m}Tc)

During cardiac nuclear imaging, the relative amount of the radioisotope that collects in the cardiac muscle is reflective of the areas of reduced blood flow and therefore areas of ischemia.[3] This information can be used to help inform disease management and to determine risk for short- or long-term future cardiac events.[3] The basic principle of radionuclide MPI is to administer a tracer labelled with a radioisotope (often thallium-201 [^{201}Tl] or technetium-99m [^{99m}Tc] sestamibi or tetrafosmin) intravenously and image blood flow to the heart muscle (myocardial perfusion), both at rest and under stress conditions. Stress is induced by either exercise or a pharmaceutical agent (e.g., dobutamine, dipyridamole, or adenosine), which increases coronary blood flow to the myocardium.[4] Viable myocardial cells take up the radionuclide tracer in proportion to blood flow.[4,5] Through sequential image acquisition, the gamma camera works with a computer to evaluate perfusion of the cardiac muscle.[6]

Comparators: For this report, the following diagnostic tests are considered as alternatives to MPI using ^{99m}Tc:

- *Computed tomography (CT) angiography (CTA)*: In a CT scan, a rotating X-ray device moves around the patient and takes detailed multiple images of organs and body parts[7] and reconstructs them into a three-dimensional (3-D) image. This series of X-rays images are often referred to as “slices,” and are taken from varying angles in order to reconstruct a 3-D

image of the heart's anatomy. A contrast agent is administered intravenously before images are taken, to better visualize the body part being examined;[7] a sedative may also be administered if the patient is uncomfortable.[8]

- *Stress echocardiogram (Echo, ECG; also called stress test)*: During stress Echo, adhesive electrodes are placed onto the bare chest of the patient and a sonographer takes several ultrasound (U/S) images of the heart while the patient is at rest. Blood pressure and Echo recordings are also measured at rest. The exercise-induced phase involves the patient engaging in physical activity (e.g., walking or running on the treadmill, pedalling a stationary bike) and the recording of blood pressure. In some cases when exercise is not an option for the patient, a pharmacological stressor may be used to simulate the stress of exercise. Following the stress phase, the patient is instructed to lie down again, and U/S images of the heart are taken a second time, as are blood pressure and Echo measurements.[9]
- *Stress MPI using ^{201}Tl:* The procedure for ^{201}Tl-SPECT is the same as ^{99m}Tc-SPECT, except the isotope ^{201}Tl is used in place of ^{99m}Tc.
- *Stress magnetic resonance imaging (MRI)*: A cardiac MRI uses magnets and a computer to reproduce images of the organs and tissues while the heart is beating.[10] As with other cardiac imaging approaches, patients are assessed under rest and stress conditions. During an MRI examination, a patient is required to lie down on a table that glides into the scanner's cavity. The patient is required to lie still for the duration of the examination, which ranges from 15 minutes to over an hour.[11]
- *Stress positron emission tomography (PET):* PET perfusion studies use radiopharmaceuticals (Rubidium-82 chloride, ^{15}O-labelled water, and ^{13}N-labelled ammonia [$^{13}NH_3$]) to visualize how well blood flows to the heart. The radiopharmaceutical is administered intravenously while the patient lies under the camera. Images are then taken for 10 to 20 minutes. To induce stress-related symptoms, a drug (e.g., dobutamine, dipyridamole, or adenosine) is administered. The patient lies still again for 10 to 20 minutes while additional images are taken. A second drug (aminophylline) is given at the end of the test to reverse the effects of the pharmacological stressor. The total duration of the test is approximately one hour.[12]

It is recognized that treadmill alone may be sufficient to diagnose ischemia, in some cases. For the purpose of this report, however, we have assumed that the need for imaging has been pre-determined. Treadmill testing, therefore, is not included as a comparator in this report.

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test

- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records & daily updates via Ovid; The Cochrane Library (2011, Issue 3) via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and myocardial ischemia.

Methodological filters were applied to limit retrieval to health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), and diagnostic accuracy studies (primary studies of randomized and non-randomized design). Where possible, retrieval was limited to the human population. The search was also limited to the English language. No date limits were applied for the systematic review search. The primary studies search was limited to the human population and to documents published between January 1, 2006 and March 29, 2011. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

The literature search identified 131 health technology assessments/systematic reviews/meta-analyses and 1,107 primary studies. Forty-one of the 131 health technology assessments/systematic reviews/meta-analyses (HTA/SR/MA) articles identified underwent full-text screening. These included a series of seven reports published in 2010 from the Ontario Ministry of Health and Long-Term Care Medical Advisory Secretariat (MAS)[13-19] to assist the Ministry in providing an evidentiary platform for the effectiveness and cost-effectiveness of non-invasive cardiac imaging technologies. These reports were reviewed and summarized, as each consisted of a meta-analysis of research from over the past six to seven years (2004 to 2009).

One-hundred and thirty-eight of the 1,107 primary studies identified in the search underwent full-text screening. A total of 17 studies related to the criterion of diagnostic accuracy were included in the final report.[20-36] For the detection of ischemia, primary studies were excluded if they were published before the search date for the MAS reports (i.e., eligible for inclusion in the MAS report), with the exception of: primary studies comparing ^{99m}Tc-based imaging to PET imaging, as this was not an eligible comparison in the MAS reports; if sensitivity and specificity outcomes were not reported; if the purpose of the study was to evaluate the accuracy of SPECT using ^{99m}Tc alone and in combination with another imaging modality (e.g., ^{99m}Tc-SPECT versus ^{99m}Tc-SPECT/CT), if both ^{99m}Tc-SPECT and ^{201}TI-SPECT were used in a study and separate analyses for the isotopes were not provided; or, if the primary study was already evaluated in one of the five MAS reports. For the evaluation of myocardial viability, inclusion was limited to studies in which ^{99m}Tc-based imaging was compared directly with another cardiac imaging modality. Studies that were included in the MAS reports on myocardial viability on MRI and PET were not assessed separately in the current report.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	No precise estimates were found as to the size of the patient population which may potentially undergo cardiac imaging for the diagnosis of ischemia. According to the CIHI Hospital Morbidity Database, in 2005/06, there were 160,323 hospitalizations with ischemic heart disease, corresponding to a crude rate hospitalization rate of 494.5 per 100,000 population (age-standardized rate = approximately 400 hospitalizations per 100,000 Canadians).[37] The 2007 CCHS found that 4.8% of the Canadian population aged 12 years and older reported having heart disease (including heart attack, angina, and congestive heart failure) diagnosed by a health professional.[37] Based on the limited evidence available, the size of the affected population is more than 1 in 1,000 (0.1%) and less than 1 in 100 (1%).
2	**Timeliness and urgency of test results in planning patient management**	The Wait Time Alliance has published benchmarks for cardiac nuclear imaging — immediate to 24 hours for emergent cases, within three days for urgent cases, and within 14 days for scheduled cases.[38] According to urgency classifications developed by the Saskatchewan Ministry of Health, MPI for detection of CAD in cases of acute chest pain without ST-elevation and negative enzymes should be conducted within two to seven days of the request for imaging (Patrick Au, Acute & Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). MPI for other indications should be conducted within eight to 30 days of the request for imaging (Patrick Au, Acute & Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). Imaging results have a moderate impact on patient management.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	Limited information was available to directly inform this criterion. Not performing a diagnostic imaging test to diagnose a suspected case of CAD in a person deemed to be at high risk of an ischemic event could result in the patient not receiving the appropriate treatment in a timely manner. However, the impact on not performing a diagnostic imaging test on a low-risk individual would likely be low. On average, diagnostic imaging results can have a moderate impact on mortality

Domain 1: Criteria Related to the Underlying Health Condition		
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Overall, limited information was available to directly inform this criterion. The impact of not performing a diagnostic imaging test to diagnose a suspected case of CAD in a person deemed to be at high risk of an ischemic event would likely be significant. However, the impact on not performing a diagnostic imaging test on low-risk individuals would likely be low. Patients with known CAD who did not receive a diagnostic imaging test to assist in risk stratification for treatment planning purposes might not receive the appropriate treatment in a timely manner. If a diagnostic imaging test to assess myocardial viability is not performed, patients with viable myocardium would not benefit from revascularization procedures. If the revascularization procedure was performed without diagnostic imaging information (i.e., with the assumption there was viable myocardium), some patients who did not have viable myocardial tissue would undergo the invasive procedure unnecessarily. It is assumed that diagnostic imaging test results can have a moderate impact on morbidity or quality of life.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	A 2004 British study compared patient satisfaction and preference toward SPECT versus MRI adenosine stress myocardial perfusion scans and found little difference.[39] The only statistically significant finding was that the SPECT scan was preferred in terms of space on the scanner.[39] Three participants (9%) stated that they would not have an MRI again, while two patients (6%) said they would not repeat a SPECT.[39] The study authors recognized that the relatively small sample size may have affected their ability to demonstrate a statistically significant preference for one scan over the other.[39] Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. Patients undergoing a CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. Patients may also need to take heart rate–lowering medication in order to undergo the test. Stress Echo may preferred by some patients, as there is no radiation exposure with it. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[40,41] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

With PET, patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. The stress PET exam is shorter than the SPECT exam.

SPECT stress MPI with ^{99m}Tc-labelled radiotracers:
• is minimally less acceptable than CTCA
• is minimally less acceptable than stress Echo
• has similar acceptability as stress MRI
• is minimally less acceptable than stress PET
• has similar acceptability as stress ^{201}Tl-SPECT.</td></tr>
<tr><td>**7**</td><td>**Relative diagnostic accuracy of the test**</td><td>The MAS of the Ontario MOHLTC conducted an evidence-based review of the literature surrounding cardiac imaging modalities.[13-19] ^{99m}Tc-SPECT, ^{201}Tl-SPECT, stress Echo, contrast Echo, CTA, and stress MRI were compared relative to CA, on the basis of their ability to diagnose CAD.[13-17]
<table>
<tr><th colspan="4">Diagnostic Accuracy: Diagnosis of CAD</th></tr>
<tr><th>Test</th><th>No. of Trials (Patients)</th><th>Pooled Sensitivity (%)</th><th>Pooled Specificity (%)</th></tr>
<tr><td>^{99m}Tc -SPECT[17]</td><td>39 (3,488)</td><td>88</td><td>70</td></tr>
<tr><td>^{201}Tl-SPECT[17]</td><td>24 (3,338)</td><td>84</td><td>71</td></tr>
<tr><td>Stress Echo[14]</td><td>127* (13,035)</td><td>80</td><td>84</td></tr>
<tr><td rowspan="3">Contrast Echo[13]</td><td>11 (patients with suspected CAD)</td><td>87.3</td><td>86.0</td></tr>
<tr><td rowspan="2">12 (patients with known or suspected CAD) (6 MPA and 6 WMA)</td><td>MPA: 87.8</td><td>MPA: 64.9</td></tr>
<tr><td>WMA: 69.2</td><td>WMA: 79.4</td></tr>
<tr><td rowspan="2">64-slice CTA[14]</td><td>8 trials</td><td>97.7</td><td>78.8</td></tr>
<tr><td>OMCAS trial (117 patients)</td><td>81.2</td><td>95.8</td></tr>
</table></td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses

Criterion	Synthesized Information

	8 studies + OMCAS trial	96.1	81.5
Stress MRI[15]	One MA + 11 studies	MPA: 91	MPA: 81
		WMA: 83	WMA: 86

CA = coronary angiography; CAD = coronary artery disease; CTA = computed tomography angiography; Echo = echocardiogram; MA = myocardial angiography; MPA = myocardial perfusion angiography; MRI = magnetic resonance imaging; OMCAS = Ontario Multidetector Coronary Angiography Study; ^{99m}Tc = Technitium-99m; ^{201}Tl =Thallium-201; SPECT = single-photon emission computed tomography; WMA = wall motion analysis.
* A study was counted twice if data were reported on different stress agents.

Our search for studies published after August 2009 identified five studies on the relative diagnostic accuracy of ^{99m}Tc-SPECT, for diagnosis of ischemia.[20-22,27,28] In addition, four studies[23-26] reported the diagnostic accuracy of one or more comparators in the diagnosis of ischemia, using ^{99m}Tc–SPECT as the gold standard.

Primary Studies: Diagnostic Accuracy: Diagnosis of CAD

Author, Date	n	Gold Standard	Intervention	Sens (%)	Spec (%)	PPV (%)	NPV (%)
^{99m}Tc-SPECT/CTA versus CA							
Kong et al., 2011[20]	104	ICA	^{99m}Tc sestamibi SPECT/CTA 3-D fusion	100	80.8	94	100
Weustink et al., 2011[21]	61	ICA	^{99m}Tc sestamibi SPECT/CTCA	89	77	91	72
			CTCA	98	82	93	93
Lu et al., 2010[22]	76	ICA	^{99m}Tc sestamibi SPECT	90	53	57	89
			Dipyridamole Echo	61	91	83	77
			Dobutamine Echo	87	82	77	90
CTCA versus ^{99m}Tc-SPECT							
Cheng et al., 2010[23]	55	^{99m}Tc tetrofosmin SPECT	Dual source CTCA	59	89	NR	NR

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses

Criterion		Synthesized Information

<table>
<tr><td>Bauer et al., 2009[24]</td><td>72</td><td>^{99m}Tc tetrofosmin SPECT</td><td>64-MDCT (> 50% stenosis)</td><td>46</td><td>83</td><td>58</td><td>75</td></tr>
<tr><td>Ruzsics et al., 2009[25]</td><td>36</td><td>^{99m}Tc tetrofosmin SPECT</td><td>Dual source CTCA</td><td>97</td><td>67</td><td>93</td><td>80</td></tr>
<tr><td colspan="8">Stress Echo versus ^{99m}Tc-SPECT</td></tr>
<tr><td>Abdelmoneim et al., 2010[26]</td><td>88</td><td>^{99m}Tc sestamibi SPECT</td><td>Adenosine stress Echo</td><td>88</td><td>85</td><td>NR</td><td>NR</td></tr>
<tr><td colspan="8">^{99m}Tc-SPECT versus PET</td></tr>
<tr><td rowspan="2">Husmann et al., 2008[27]</td><td rowspan="2">80 (SPECT) 70 (PET)</td><td rowspan="2">ICA</td><td>^{201}TICI SPECT or ^{99m}Tc-MIBI SPECT</td><td>85</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td>Attenuation- corrected $^{13}NH_3$ PET</td><td>96</td><td>NR</td><td>NR</td><td>NR</td></tr>
<tr><td rowspan="2">Bateman et al., 2006[28]</td><td rowspan="2">112</td><td rowspan="2">Clinical coronary angiogram reports</td><td>^{99m}Tc sestamibi SPECT</td><td>82</td><td>73</td><td>NR</td><td>NR</td></tr>
<tr><td>^{82}Rb-PET</td><td>87</td><td>93</td><td>NR</td><td>NR</td></tr>
</table>

CA = coronary angiography; CAD = coronary artery disease; CTA = computed tomography angiography; CTCA = computed tomography coronary angiography; Echo = echocardiography; ICA = invasive coronary angiography; MDCT= multidetector computed tomography; n = number of patients; $^{13}NH_3$ = 13N-labelled ammonia; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technitium-99m; ^{201}Tl =Thallium-201; ^{201}TICI = thallium-201 chloride; ^{99m}Tc-MIBI = ^{99m}Tc-sestamibi (technetium-99m-hexakismethoxy-isobutyl-isonitril).

Based on the available evidence, the diagnostic accuracy of ^{99m}Tc-SPECT MPI is:

- minimally higher than stress CTCA
- similar to stress Echo
- minimally lower than stress MRI
- minimally lower than stress PET
- minimally higher than ^{201}TI-SPECT stress imaging.

8	**Relative risks associated with the**	**Non–radiation-related risks**

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
	test	The main risks of non-invasive preoperative assessment relate to the stress component of the tests. With exercise stress testing, there is a small risk of the patients sustaining an MI if they have significant coronary artery disease.[42] With dipyridamole stress testing, there are multiple potential side effects, including headache, exacerbated asthma, and heart attack (risk of this event is low).[42] With adenosine stress testing, side effects similar to dipyridamole may be experienced. Symptoms of chest pain or pressure may also occur, but these side effects quickly disappear once the adenosine administration stops.[42] With dobutamine stress testing, some patients may experience light-headedness and nausea. There is a theoretical risk of inducing a fast and abnormal cardiac rhythm (i.e., atrial fibrillation, ventricular tachycardia, ventricular fibrillation); however, this is unlikely with the doses of dobutamine used. The overall risk of sustaining a heart attack from a stress test is estimated to be about 2 to 4 in 10,000.[42] Apart from risks associated with stress testing, the radiopharmaceuticals used in SPECT imaging may cause reactions in some patients. These reactions are rare and include skin and anaphylactic reactions.[43] With CTCA, some patients may experience mild, moderate, or severe side effects from the contrast. The frequency of severe, life-threatening reactions with gadolinium are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions range are also rare (0.004% to 0.7%).[44] Apart from risks associated with stress testing, there is a low risk of adverse events associated with the contrast used in stress Echo imaging. Apart from risks associated with stress testing, some patients may experience a reaction to the contrast agent Gd used in MRI. Reactions may include headaches, nausea, and metallic taste. The frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions range are also rare (0.004% to 0.7%)[44] Apart from risks associated with stress testing, the Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[45] The risks associated with stress testing would apply for cardiac imaging using PET. **Radiation-related Risks** Among the modalities to diagnose ischemia, SPECT MPI, CTCA, and stress PET expose the patient

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in the subsequent table.
<table>
<tr><th colspan="2">Effective Doses of Radiation</th></tr>
<tr><th>Procedure</th><th>Average Effective Dose (mSv)</th></tr>
<tr><td>^{99m}Tc-SPECT MPI</td><td>7 to 12.8[46]</td></tr>
<tr><td>^{201}Tl-SPECT MPI</td><td>17 to 41[46,47]</td></tr>
<tr><td>Cardiac ^{18}FDG-PET</td><td>7(MIIMAC expert opinion) to 14 [47]</td></tr>
<tr><td>Cardiac ^{82}Rb-PET</td><td>1.1 to 5.0[47-49]</td></tr>
<tr><td>Cardiac $^{13}NH_3$-PET</td><td>1.5 to 2.2[49]</td></tr>
<tr><td>CTCA</td><td>2.1 to 16[50,51]</td></tr>
<tr><td>MRI</td><td>0</td></tr>
<tr><td>Echo</td><td>0</td></tr>
<tr><td>Average background dose of radiation per year</td><td>1-3.0[52-54]</td></tr>
</table>
CTCA = computed tomography coronary angiography; CMPI = myocardial perfusion imaging; Echo = echocardiogram; ^{18}FDG =18F-fluorodeoxyglucose; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; MRI = magnetic resonance imaging; mSv = millisievert; $^{13}NH_3$ = 13N-labelled ammonia; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technitium-99m.

Overall, ^{99m}Tc-SPECT MPI:
• and CTCA have similar safety profiles
• and stress Echo have similar safety profiles
• and stress MRI have similar safety profiles
• and stress PET have similar safety profiles
• and ^{201}TI-SPECT have similar safety profiles.</td></tr>
<tr><td>**9**</td><td>**Relative availability of personnel with expertise and experience required for the test**</td><td>In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic nuclear imaging, CT scans, MRI, and U/S should be diagnostic radiologists or nuclear medical physicians. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). Not all radiologists, nuclear medical physicians, nuclear cardiologists, or cardiologists have the expertise to conduct ^{99m}Tc-SPECT and all of its alternatives. For example, a 2002 report by the CCS reported that 43% of cardiologists do Echo.

Assuming the necessary equipment is available, if ^{99m}Tc-SPECT imaging is not available, it is estimated that:</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		• 25% to 74% of the procedures can be performed in a timely manner using CTCA • 25% to 74% of the procedures can be performed in a timely manner using Echo • fewer than 25% of the procedures can be performed in a timely manner using MRI • 25% to 74% of the procedures can be performed in a timely manner using PET • more than 95% of the procedures can be performed in a timely manner using ^{201}TI-SPECT.
10	**Accessibility of alternative tests (equipment and wait times)**	For SPECT MPI, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of 2007, no nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[55] No CT scanners are available in Nunavut.[56] For CT scanners, the average weekly use ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[55] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[57] The average wait time for a CTCA was not reported. Of note, not all CT scanners are capable of performing cardiac CT. No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[56] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[55] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[57] A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[58] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[58] There are a total of 36 PET or PET/CT scanners in Canada, four of which are used for research purposes only.[58] U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[57] Assuming the necessary personnel is available, if ^{99m}Tc-SPECT imaging is not available, it is estimated that: • 25% to 74% of the procedures can be performed in a timely manner using CTCA • 75% to 94% of the procedures can be performed in a timely manner using Echo • fewer than 25% of the procedures can be performed in a timely manner using MRI • fewer than 25% of the procedures can be performed in a timely manner using PET • more than 95% of the procedures can be performed in a timely manner using ^{201}TI-SPECT.
11	**Relative cost of the test**	According to our estimates, the cost of MPI with ^{99m}Tc-based radioisotopes is $964.53. The cost of MPI with ^{201}TI or with PET is assumed to be greater than imaging with ^{99m}Tc-based radioisotopes.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		Stress MRI is minimally less costly than MPI with ^{99m}Tc. CTCA and stress Echo are moderately less costly.

Relative Costs

Test	Total Costs ($)	Cost of Test Relative to ^{99m}Tc-based Test ($)
^{99m}Tc-SPECT MPI	964.53	Reference
^{201}TI-SPECT MPI	964.53	+0.00
CTCA	506.03	-458.50
Stress Echo	466.90	-497.63
Stress MRI	835.16	-129.37
Stress PET	1128.60	+164.07

CA = coronary angiography; CAD = coronary artery disease; CCHS = Canadian Community Health Survey; CCS = Canadian Cardiovascular Society; CIHI = Canadian Institute for Health Information; CMA = Canadian Medical Association; CT = computed tomography; CTA = computed tomography angiography; CTCA = computed tomography coronary angiography; Echo = echocardiography ECG = electrocardiogram; ^{18}FDG-PET = ^{18}fluorodeoxyglucose-positron emission tomography; ICA = invasive coronary angiography; MAS = Medical Advisory Secretariat; MDCT = multidetector computed tomography; MI = myocardial infarction; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; MOHLTC = Ministry of Health and Long-Term Care; MPA = myocardial perfusion analyses; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; mSv = millisievert; NA= not available; $^{13}NH_3$ = 13N-labelled ammonia; OMCAS = Ontario Multidetector Coronary Angiography; PHAC = Public Health Agency of Canada; PEI = Prince Edward Island; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technitium-99m; ^{99m}Tc-MIBI = ^{99m}Tc-sestamibi (^{99m}Tc-MIBI = ^{99m}Tc-sestamibi (technetium-99m-hexakismethoxy-isobutyl-isonitril); ^{201}Tl =Thallium-201; U/S = ultrasound; WMA = wall motion analyses.

CRITERION 1: Size of affected population (link to definition)

No precise estimates were found as to the size of the patient population which may potentially undergo cardiac imaging for the diagnosis of ischemia or the evaluation of myocardial viability.

According to the Canadian Institute for Health Information (CIHI) Hospital Morbidity Database, in 2005–2006, there were 160,323 hospitalizations, with ischemic heart disease as the condition most responsible for them; this corresponds to a crude rate hospitalization rate of 494.5 per 100,000 population (age-standardized rate = approximately 400 hospitalizations per 100,000 Canadians).[37] The size of the patient population which may undergo diagnostic imaging for the diagnosis of ischemia or the evaluation of myocardial viability would likely be greater than this. Although a single patient may be hospitalized more than once in a single year (leading to overestimation), a proportion of patients with ischemia will not require hospitalization, and a further proportion of patients undergoing diagnostic imaging for the diagnosis of ischemia or the evaluation of myocardial viability will never be diagnosed with ischemia (leading to underestimation).

The Canadian Community Health Survey (CCHS) is a cross-sectional survey targeting Canadians aged 12 years and older. The 2007 CCHS found that 4.8% of the Canadian population aged 12 years and older reported having heart disease (including heart attack, angina, and congestive heart failure) diagnosed by a health professional.[37] This may be a reasonable approximation to the size of the patient population which may undergo diagnostic imaging for the diagnosis of ischemia or the evaluation of myocardial viability. Although the data are self-reported and include only those patients diagnosed by a health professional (leading to underestimation), they report on broadly-defined heart disease, including heart attack, angina, and congestive heart failure (leading to overestimation).

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

According to the Wait Time Alliance, the benchmark for cardiac nuclear imaging is: immediate to 24 hours for emergent cases, within three days for urgent cases, and within 14 days for scheduled cases.[38]

According to urgency classifications developed by the Saskatchewan Ministry of Health, MPI for the detection of CAD in cases of acute chest pain without ST-elevation and negative enzymes should be conducted within two to seven days of the request for imaging. (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011)

MPI should be conducted within eight to 30 days of the request for imaging for the following indications:

- detection of CAD (symptomatic) evaluation of ischemic equivalent (non-acute)
- detection of CAD/risk assessment without ischemic equivalent (asymptomatic)
- risk assessment with prior test results and/or known chronic stable CAD
- risk assessment within three months of acute coronary syndrome
- risk assessment post-revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG])
- and assessment of viability/ischemia in ischemic cardiomyopathy with known severe left ventrical dysfunction.

(Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011.)

Return to Summary Table

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

A report published by the Public Health Agency of Canada states that ischemic heart disease was responsible for 39,311 deaths (17.3% of all deaths) in 2004.[37] The rate of death is higher in men than in women and increases with age.

The Myoview Prognosis Registry provides data on 7,849 outpatients (from five tertiary medical centres in the United States) evaluated by stress MPI for suspected, or known, CAD.[59] A 2008 publication, based on data from this registry, investigated the relationship between cardiovascular outcomes and the extent and severity of ischemia, as well as perfusion defects on the resting MPI.[59] In two years of follow-up, 274 deaths were reported (3.5% of the study population) including 29 fatal MIs, 72 sudden cardiac deaths, 14 heart failures, and 16 fatal cerebrovascular accidents.[59] Although the study population was stratified by per cent ischemic myocardium (73% of the study cohort had 0% ischemic myocardium, 11% had 1% to 4.9% ischemic myocardium, 9% had 5% to 9.9% ischemic myocardium, and 7% had > 10% ischemic myocardium), the mortality rates for these subgroups were not reported.[59] It was noted that rest and ischemic defects on MPI were highly significant ($P < 0.0001$) estimators of the combined end point of CAD-related events (including fatal MI, non-fatal MI, and sickle-cell disease) according to univariate Cox models.[59] An earlier publication, based on this registry, reported that the annualized cardiac death rate among patients with a normal perfusion scan is less than one per cent.[60]

A 2003 publication by Hachamovitch et al.[61] compared the survival benefit associated with revascularization versus medical therapy. The final study population included 10,627 patients who underwent exercise or adenosine stress myocardial perfusion scintigraphy between 1991 and March 1997.[61] The majority (n = 9,956) were prescribed medical therapy, while 671 patients underwent early revascularization.[61] Patients were followed for an average of 1.9 years with cardiac death as the sole end point.[61] The rate of cardiac death among revascularized patients was 2.8% versus 1.3% among the medical therapy group; however, the baseline characteristics of the two groups were found to differ significantly.[61] Propensity scores were calculated, using logistic regression, in order to adjust for the lack of randomization.[61] A Cox proportional hazards model was used to predict mortality rates in patients treated with revascularization versus medical therapy.[61] The model predicted that patient mortality rates among those treated medically would increase significantly as a function of per cent myocardium ischemic, but that increased per cent myocardium ischemic would not be associated with an increase in mortality among revascularized patients (Table 2). This study highlights the importance of detecting and quantifying ischemia.

Table 2: Predicted Mortality Rates in Non-diabetic Patients Treated with Revascularization Versus Medical Therapy Based on Cox Proportional Hazards Model[61]			
	% Myocardium Ischemic		
	Small (5% to 10%)	**Moderate (10% to 20%)**	**Large (> 20%)**
Males			
Medical therapy (%)	2.5	3.4	5.1
Revascularization (%)	2.3	1.8	1.9
Lives saved per 100 patients revascularized	0.2	1.6	3.2
Females			
Medical therapy (%)	2.7	4.9	10.0
Revascularization (%)	3.9	3.7	2.5
Lives saved per 100 patients revascularized	-1.2	1.2	7.5

Overall, limited information was available to directly inform this criterion. Patients with intermediate pre-test likelihood of disease are most likely to benefit from a diagnostic and prognostic perspective, but high pre-test likelihood patients will also benefit from a prognostic perspective (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert opinion).

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

As part of a 2007 rapid systematic review and pragmatic randomized controlled trial conducted for the National Institute for Health Research in the United Kingdom on the management of CAD, Sharples et al.[62] measured the health-related quality of life of patients at a tertiary cardiothoracic referral centre in the United Kingdom with known or suspected CAD requiring non-urgent angiography.[62] The aim of the study was to determine the most cost-effective approach of the following four modalities to diagnose CAD: angiography, SPECT, MRI, and Echo. A total of 898 patients were assessed using various instruments for measuring health status. Using one of the tools — the 36-item Short Form Health Survey or SF-36 (a generic instrument containing eight domains: physical function, role-physical [limitations due to physical function], bodily pain, general health, vitality, social function, role-emotional [limitations due to emotional function], mental health — and two summary scores (physical component score and mental component score), the mean physical component scores at baseline for patients in this cohort randomized to the four modalities was statistically significantly lower than the mean for the general population ($P < 0.001$). An improvement in these scores was noted following treatment (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI], or medical).[62]

Overall, limited information was available to directly inform this criterion. The impact of not performing a diagnostic imaging test to diagnose a suspected case of CAD in a person deemed to be at high risk of an ischemic event because of a combination of clinical symptoms (including type of chest pain), clinical risk factors, and results from non-nuclear cardiac imaging tests such as an exercise stress test) would likely be significant. However, the impact on not performing a diagnostic imaging test on low-risk individuals would likely be low.

Patients with known CAD who did not receive a diagnostic imaging test to assist in risk stratification for treatment planning purposes, might not receive the appropriate treatment in a timely manner.

If a diagnostic imaging test to assess myocardial viability is not performed, patients with viable myocardium would not benefit from revascularization procedures. If the revascularization procedure was performed without diagnostic imaging information (i.e., with the assumption that there was viable myocardium), some patients who did not have viable myocardial tissue would undergo the invasive procedure unnecessarily.

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CRITERION 5: Relative impact on health disparities (link to definition)

Female gender
In a 1994 study, Shaw et al[63] recruited patients referred for exercise stress testing or intravenous dipyridamole ^{201}TI myocardial imaging with clinically suspected CAD and compared male (449) and female (n = 391) patient outcomes in the two years (24 ± 7 months) following the test.[63] While the percentages of patients with initially abnormal exercise Echo results and MPI study results were similar between the two genders, additional diagnostic testing was done in only 38.0% of women, compared with 62.3 % of men (P = 0.002).[63] The lack of follow-up testing in women was associated with worsening rates of cardiac death or MI.[63] One study comparing 100 females with disabilities to 50 females without disabilities reported that baseline risk assessments including discussions of family medical history were less likely to be performed in women with disabilities than in their non-disabled counterparts.[64]

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

SPECT
A 2004 British study compared patient satisfaction and preference toward SPECT with MRI adenosine stress myocardial perfusion scans and found little difference.[39] Forty-one patients who had undergone both SPECT and MRI were sent a retrospective questionnaire within two weeks of scan completion. Thirty-five completed questionnaires were returned. When asked “If the two tests (nuclear heart scan and MRI) could provide the same information, which of the two would you prefer?” 12 patients (34%) stated a preference for MRI, nine (26%) stated a preference for SPECT, and 14 (40%) stated no preference.[39] Patients rated the two tests similarly on overall preference, duration, comfort, and safety, with a non-significant preference for MRI on all of the afoementioned.[39] The only statistically significant finding was that the SPECT scan was preferred in terms of space on the scanner.[39] Three participants (9%) stated that they would not have an MRI again, while two patients (6%) said they would not repeat a SPECT.[39] The study authors recognized that the relatively small sample size may have affected their ability to demonstrate a statistically significant preference for one scan over the other.[39] Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Computed Tomography Coronary Angiography (CTCA)
Patients undergoing a CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion).

Stress Echo
This test is likely to be well tolerated by patients. Echo may be preferred by some patients since there is no radiation exposure. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Stress MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[40,41] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Stress PET MPI (Rubidium-82 [^{82}Rb] or 13N-labelled ammonia [$^{13}NH_3$])
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

The literature search for health technology assessments (HTA)/systematic reviews/meta-analyses identified 131 studies, five of which are included in the current report.[15-19] These HTAs evaluated the use of non-invasive cardiac imaging technologies including stress Echo (with and without contrast agent),[13,14] MRI,[15] CT,[16] and SPECT[17] for the diagnosis of CAD.

The literature search for primary studies identified 1,107 titles. When limited by date (so that only those studies published following the end of the search period of the corresponding HTA were included), 138 underwent full-text screening, and nine non-randomized studies were included in the final report.[20-28] No randomized controlled trials that met inclusion criteria were identified.

A summary of two position statements not meeting inclusion criteria — one a joint position statement published in 2007 by the Canadian Cardiovascular Society (CCS), Canadian Association of Radiologists, Canadian Association of Nuclear Medicine, Canadian Cardiovascular Society, and the Canadian Society of Cardiovascular Magnetic Resonance on the use of PET, MRI, and CT in the diagnosis of ischemic heart disease,[65] and a second released jointly in 2011 by the European Association of Nuclear Medicine, the European Society of Cardiac Radiology, and the European Council of Nuclear Cardiology on the use of hybrid cardiac imaging with SPECT or PET combined with CT (SPECT/CT, PET/CT) to image anatomical and physiologic cardiac abnormalities in a single setting[66] — is provided in Appendix 3 as background information. The Canadian position statement[65] was based on a

systematic review of the literature relating to PET, MRI, and CT; however, it did not assess ^{99m}Tc-SPECT. The European consensus statement discussed SPECT/CT hybrid technology.

Health technology assessments

In July 2009, MAS of the Ontario Ministry of Health and Long-Term Care began an evidence-based review of the literature surrounding cardiac imaging modalities. Systematic reviews, meta-analyses, randomized controlled trials, prospective observational trials, and retrospective analyses with a sample size of 20 or more patients were included; non-systematic reviews, case reports, grey literature, and abstracts were excluded. The interventions of interest were cardiac MRI, SPECT (using ^{99m}Tc or ^{201}Tl), 64-slice computed tomographic coronary angiography (CTCA), stress echocardiography, and stress echocardiography with contrast. The comparator was coronary angiography (CA). The outcomes of interest were accuracy, adverse events, and costs. The use of imaging for risk stratification purposes was not considered as part of the reports. A summary of the findings of the MAS reports on the use of non-invasive cardiac imaging technologies for the diagnosis of coronary artery disease[13-17] can be found in Appendix 4.

^{99m}Tc-SPECT MPI versus coronary angiography

A review of the literature was completed to assess the diagnostic accuracy of SPECT, in comparison to CA, for the diagnosis of CAD.[17] From the search period of January 1, 2004 to August 22, 2009, a total of 86 studies (10,870 patients) were analyzed by MAS.[17] For the purpose of this report, the results for ^{99m}Tc-SPECT and ^{201}TI-SPECT are reported separately.[17] A total of 39 (n = 3,488) studies looked exclusively at ^{99m}Tc-SPECT in comparison with CA.[17] The pooled sensitivity and specificity of ^{99m}Tc-SPECT, relative to CA, in the diagnosis of CAD were 88% and 70%, respectively.[17] It is not clear from the report whether the included studies considered recent technological advances in SPECT with attenuation correction.

The diagnostic accuracies of the five imaging modalities were calculated against the reference standard of coronary angiography; therefore, the evidence relating to each of the modalities is presented in this report.

CTCA versus CA

A review of the literature to assess the diagnostic accuracy of 64-slice CTCA, compared with CA, in the diagnosis of CAD in stable symptomatic patients was completed.[16] From the search period of January 1, 2004 to July 20, 2009, a total of eight studies (1,513 patients) were included in the review.[16] The pooled sensitivity and specificity of CTCA, relative to CA, in the diagnosis of CAD, were 97.7% and 78.8%, respectively.[16] In February 2010, results of the Ontario Multidetector Coronary Angiography Study (OMCAS) were made available.[16] This non-randomized double-blinded study (n=169) evaluated CTCA versus CA in the diagnosis of CAD and found the sensitivity of CTCA versus CA to be 81.2% and the specificity to be 95.8%.[16] When the OMCAS results were added to the MAS meta-analysis, the specificity of CTCA was greater (81.5%), while the sensitivity dropped to 96.1%.[16]

^{201}TI-SPECT MPI versus CA

A total of 24 studies (n = 3,338) included in the MAS SPECT review evaluated ^{201}TI-SPECT in comparison with CA.[17] The pooled sensitivity and specificity of ^{201}TI-SPECT, relative to CA, in the diagnosis of CAD were 84% and 71%, respectively.[17]

Stress Echo (with and without contrast) versus CA

A review of the literature was completed to assess the diagnostic accuracy of stress Echo, in comparison with CA, for the diagnosis of CAD.[14] From the search period of January 1, 2004 to August 22, 2009, 127 studies (13,035 patients) were included in the review.[14] The available evidence was pooled and the overall results indicated a sensitivity of 80% and a specificity of 84%.[14] These estimates may not be generalizable outside of the setting of a strong research laboratory as stress Echo has been associated with low reproducibility (MIIMAC expert opinion).

A second report published by MAS evaluated contrast Echo, in comparison with CA, for the diagnosis of CAD.[13] In patients with suspected CAD, in only (11 studies), the pooled sensitivity and specificity were 87%, and 86%, respectively.[13] Twelve studies evaluated the diagnostic accuracy of contrast Echo in patients with suspected or known CAD — six based on myocardial perfusion analysis (MPA) and six based on wall motion analysis (WMA).[13] When results from the MPA studies were pooled, the sensitivity was 88% and the specificity was 65%.[13] The pooled WMA results indicated a sensitivity of 69% and a specificity of 79%.[13]

Stress MRI versus CA

A review of the literature was completed to assess the diagnostic accuracy of stress MRI, compared with CA, in the diagnosis of CAD.[15] From the search period of January 1, 2005 to October 9, 2008, one meta-analysis and 11 primary studies were found.[15] The studies from the meta-analysis were pooled with the new literature for a total of 37 studies using MPA and WMA imaging.[15] The pooled results for diagnostic accuracy including MPA produced a sensitivity of 91% and a specificity of 79%.[15] Regarding the WMA, the pooled sensitivity and specificity were 81% and 85%.[15]

Primary studies

The MAS report reviewed the available literature for the diagnostic accuracy of SPECT in comparison with CA for the diagnosis of CAD (January 1, 2004 to August 22, 2009). A search for studies published after August 2009 identified five studies on the relative diagnostic accuracy of ^{99m}Tc-SPECT, as it pertains to the diagnosis of ischemia.[20-22,27,28] In addition, four studies[23-26] reported the diagnostic accuracy of one or more comparators in the diagnosis of ischemia, using ^{99m}Tc–SPECT as the gold standard.

^{99m}Tc-SPECT/CTA versus CA

A recent study by Kong et al. (2011)[20] compared the diagnostic accuracy of ^{99m}Tc sestamibi SPECT/CTA 3-D fusion with that of invasive CA.[20] One-hundred and four patients (mean age: 63.6 years) with typical or atypical angina symptoms were included in this retrospective analysis.[20] SPECT/CTA, in comparison with CA, yielded a sensitivity of 100% and a specificity of 80.8%.[20] The positive predictive value and the negative predictive value of the test were 94% and 100%, respectively.[20] The authors stated that the results of this study support the use of SPECT/CTA for the diagnosis of CAD.[20]

Also in 2011, Weustink et al.[21] compared the diagnostic accuracy of bicycle testing/ CTCA (also referred to as CTA) and ^{99m}Tc-sestamibi SPECT/CTCA in the diagnosis of CAD, using invasive CA as the gold standard.[21] Three-hundred and seventy-six symptomatic patients (mean age: 60.4) participated in the study.[21] A comparison between bicycle testing and SPECT was not made. In patients who underwent SPECT (n = 61), the sensitivity of SPECT (89%) was found to be statistically significantly less than that of CTCA (98%) (P= 0.021). CTCA was more specific than SPECT (82% compared to 77%), but this difference was not statistically significant (P =

1.0).[21] The authors concluded that the results of this study demonstrate a high diagnostic performance for CT and SPECT.[21]

^{99m}Tc –SPECT and stress Echo versus CA

In 2010, Lu et al.[22] evaluated the diagnostic accuracy of SPECT (^{99m}Tc sestamibi), stress Echo (dipyridamole and dobutamine), and CA for the detection of CAD in a population of 76 female hypertensive patients (mean age: 60 years) with no previous MI or history of CAD.[22] CA was used as the reference standard.[22] The results of this prospective study are provided in Table 3. The authors suggested that, based on these results, dobutamine Echo should be used as a first-line diagnostic in women with suspected CAD, due to its high diagnostic value.[22]

Table 3: Relative Diagnostic Accuracy of SPECT and Echo for the Diagnosis of CAD in Female Hypertensive Patients[22]

	Sensitivity	Specificity	Accuracy	Positive Predictive Value	Negative Predictive Value
SPECT	90	53	68	57	89
Dipyridamole Echo	61	91	79	83	77
Dobutamine Echo	87	82	84	77	90

CAD = coronary artery disease; Echo = echocardiography; SPECT = single-photon emission tomography.

CTCA versus ^{99m}Tc –SPECT

A 2010 study by Cheng et al.[23] compared the relative diagnostic accuracy of dual-source CTCA (DS-CTCA) to gated SPECT (^{99m}Tc tetrofosmin). A total of 55 patients had clinical symptoms of CAD (e.g., chest pain, shortness of breath), were asymptomatic but had risk factors, or had known CAD.[23] The mean age of the population was 60.7 years and the majority of the patients were male (58%).[23] All patients underwent both ^{99m}Tc –SPECT and DS-CTCA.[23] A diagnosis of CAD was noted on the DS-CTCA if stenosis was a minimum of 50%, and was compared with SPECT at rest and during stress.[23] Compared to SPECT at rest, the sensitivity, specificity, and accuracy of DS-CTCA were 100%, 78%, and 83.6%.[23] Compared to SPECT using stress conditions, the sensitivity, specificity, and accuracy of DS-CTCA were 83.3%, 90.3%, and 87.3%.[23] However, when rest/stress-SPECT was used as the reference standard, the sensitivity of DS-CTCA to detect high-grade stenosis (a minimum of 50%) was 59% and the specificity was 89%. There was a lack of correlation between DS-CTCA and SPECT findings. The authors concluded that DS-CTCA may provide additional information regarding perfusion defects first identified by ^{99m}Tc-SPECT.

A 2009 study by Bauer et al.[24] was conducted to determine the correlation between the diagnostic accuracy of 64-slice multidetector computed tomography (MDCT, referred to as CT) readings of calcification in comparison with ischemia detected by ^{99m}Tc-SPECT with ^{99m}Tc tetrofosmin.[24] Seventy-two patients with known (n = 23) or suspected (n = 49) CAD underwent CT angiography and stress-rest SPECT.[24] Stenosis was classified as insignificant (< 50%), significant (≥ 50%), or severe (≥ 70%) based on CT imaging.[24] SPECT images were reviewed for the presence of reversible and fixed perfusion defects.[24] Patient-based and vessel-based results were presented.[24] When the diagnostic outcomes were evaluated at the patient level for any perfusion defect on SPECT and ≥ 50% stenosis on CT, the sensitivity and specificity were 46% and 83%.[24] When the diagnostic outcomes were evaluated at the patient level for any perfusion defect on SPECT and ≥ 70% stenosis on CT, the sensitivity and specificity were 38%

and 98%, respectively.[24] When the data was evaluated for reversible perfusion defects on SPECT compared with ≥50% stenosis on CT, the sensitivity and specificity were 33% and 83%, respectively.[24] The comparison between ≥ 70% stenosis on CT and the presence of reversible perfusion defects on SPECT provided a sensitivity estimate of 25% and specificity estimate of 98%.[24] The authors concluded that the degree of stenosis as determined by CT was not a reliable predictor of ischemia at stress-rest SPECT in this heterogeneous, clinically-representative patient group.[24]

The performance of dual source dual energy computed tomography (DECT) for the integrative imaging of the coronary arteries was evaluated by Ruzsics et al.[25] in 2009. A total of 36 patients with known (n = 9) or suspected (n = 27) CAD were evaluated for a diagnosis of CAD with stenosis ≥ 50%.[25] DECT and ^{99m}Tc-SPECT with tetrofosmin were performed in all patients and the images were compared for perfusion defects (fixed and reversible).[25] When the diagnostic outcomes were evaluated at the patient level for any perfusion defect on SPECT and ≥ 50% stenosis on CT, the sensitivity and specificity were 97% and 67% (as in Table 6).[25] When the data were evaluated for reversible perfusion defects on SPECT compared with ≥ 50% stenosis on CT, the sensitivity and specificity were 100% and 67%.[25] Data evaluated for fixed perfusion defects on SPECT compared with ≥ 50% stenosis on CT provided a sensitivity estimate of 94% and a specificity estimate of 67%.[25] The authors noted that, although their findings for DECT compared with SPECT were favourable, the study was limited by the small sample size and a higher prevalence of CAD than would be found in the general population.[25]

Stress Echo versus ^{99m}Tc –SPECT

Abdelmoneim et al.[26] evaluated the diagnostic accuracy of stress Echo, compared with SPECT (^{99m}Tc sestamibi). Patients (n = 88) with known or suspected CAD underwent both stress Echo (adenosine) with contrast and SPECT.[26] The images for both tests were interpreted and compared.[26] Coronary deficiencies in Echo were interpreted by wall motion analysis (WMA) or real-time perfusion using myocardial contrast echocardiography (MCE) techniques.[26] In total, 88 patients were included in the final analysis of MCE and 73 patients for final analysis of WMA.[26] In comparison with SPECT, the sensitivity and specificity of stress Echo were determined to be 88% and 85%.[26] The authors concluded that adenosine MCE in real time is effective in the detection of myocardial defects.[26]

^{99m}Tc-SPECT versus PET

Husmann et al.[27] compared the diagnostic accuracy of MPI with PET or SPECT in two comparable patient cohorts with known or suspected CAD, using coronary angiography as the gold standard. The SPECT group consisted of 80 patients (15 female, 65 male; mean age 60 ± 9 years) and the $^{13}NH_3$-PET group consisted of 70 patients (14 female, 56 male; mean age 57 ± 10 years). The SPECT group included patients who received either ^{201}Tl chloride or ^{99m}Tc sestamibi. Coronary angiography findings did not significantly differ between groups. All patients underwent a one-day stress/rest protocol. PET and SPECT images were transferred to external workstations and evaluated by two independent observers blinded to results of the angiography. In the detection of CAD, the overall sensitivity of SPECT was 85% compared with 96% for PET. For the SPECT group, the overall sensitivity and specificity for localization of stensosis was 77% and 84%, respectively. Comparatively, in the PET group, the sensitivity was 97% and the specificity 84%. For the detection of ischemia, the specificity was 74% for SPECT and 91% for PET. Husmann et al. concluded that MPI with $^{13}NH_3$-PET is more sensitive in the detection and localization of coronary stenosis, and more specific in the detection of ischemia than MPI using SPECT with either ^{99m}Tc or ^{201}Tl. The Husmann et al. study was included in this report despite the fact that the authors did not provide separate analyses for ^{99m}Tc and ^{201}Tl. It is possible that

the sensitivity and specificity of ^{99m}Tc is lower or higher than the pooled value. This study was included based on the limited available information for comparing ^{99m}Tc-based imaging to PET; however, the limitations of the study should be noted.

Bateman et al. (2006)[28] compared the diagnostic accuracy of ^{99m}Tc sestamibi SPECT and ^{82}Rb-PET for MPI of patients matched by gender, body mass index, and presence and extent of coronary disease.[28] Included patients were identified retrospectively from an electronic nuclear cardiology database and were categorized as having a low likelihood for CAD (n = 27) or had coronary angiography within 60 days (n = 27). Four experienced nuclear medicine cardiologists blinded to patients' clinical information interpreted scans obtained from 112 ^{99m}Tc-SPECT and 112 ^{82}Rb-PET Echo-gated rest/pharmacologic stress studies. By consensus, the quality of the perfusion images were deemed superior with PET (78% and 79% for rest and stress scans, respectively) than SPECT (62% and 62%; both P > 0.05). Interpretive certainty was also rated higher with PET versus SPECT scans (96% versus 81%, P = 0.001). Diagnostic accuracy was better for PET over SPECT — for patients with a stenosis severity of 70% by angiography, the sensitivity was 82% for SPECT and 87% for PET (P = 0.41) and the specificity was 73% for SPECT versus 93% for PET (P = 0.02), resulting in a significant improvement in overall accuracy by PET (89% versus 79%, P = 0.03). For patients with 50% stenosis, the respective comparative accuracy was 71% for SPECT versus 87% for PET (P = 0.003). Bateman and colleagues conclude that for this patient population, a major benefit of PET over SPECT is higher diagnostic accuracy.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related risks

Cardiac Stress Tests
The main risks of non-invasive preoperative assessment relate to the stress component of the tests:

- With exercise stress testing, there is a small risk of the patient sustaining an MI if they have significant coronary artery disease.[42]
- With dipyridamole stress testing, there are multiple potential side effects, including headache, exacerbated asthma, and heart attack (risk of this event is low).[42]
- With adenosine stress testing, side effects similar to dipyridamole may be experienced. Symptoms of chest pain or pressure may also occur, but these side effects go away quickly once the adenosine administration stops.[42]
- With dobutamine stress testing, some patients may experience light-headedness and nausea. There is a theoretical risk of inducing a fast and abnormal cardiac rhythm (i.e., atrial fibrillation, ventricular tachycardia, ventricular fibrillation); however, this is unlikely with the doses of dobutamine used. A slight risk of MI exists.[42]

The overall risk of sustaining a heart attack from a stress test is estimated to be about 2 to 4 in 10,000.[42]

Stress SPECT
Apart from risks associated with stress testing, a review of undesirable events with radiopharmaceuticals reported anaphylactic reactions and erythema multiforme (i.e., a type of skin reaction) with sestamibi, although these reactions may be rare.[43]

CTCA

Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[67] In addition, patients may experience mild side effects such as nausea, vomiting, or hives from the contrast agent. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium (Gd) contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found that 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[68] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. Patients must be able to take rate-lowering medications. Although rarely used in cardiac imaging, Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[44] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[44]

Stress Echo

Apart from risks associated with stress testing, three relatively large studies — with sample sizes of 42,408 patients (2009),[69] 26,774 patients (2009),[70] and 5069 patients (2008)[71] — compared cardiac outcomes (non-fatal MI or death) between patients who underwent contrast-enhanced Echo with patients who had an Echo without contrast. All three studies concluded that the risk of an adverse event is low and is no different than for patients who received no contrast. No additional risks associated with Echo were identifed.

Stress MRI

Apart from risks associated with stress testing, MRI is contraindicated in patients with metallic implants including pacemakers.[72] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[67] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[44] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[44]

Stress PET

The Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[45] The risks associated with stress testing would apply for cardiac imaging using PET.

Radiation-related Risks

Among the modalities to diagnose ischemia, SPECT MPI, CTCA, and stress PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 4.

Table 4: Effective Doses of Radiation	
Procedure	**Average Effective Dose (mSv)**
^{99m}Tc-SPECT MPI	7 to 12.8[46]
^{201}Tl-SPECT MPI	17 to 41[46,47]
Cardiac ^{18}FDG-PET	7 (MIIMAC expert opinion) to 14[47]
Cardiac ^{82}Rb-PET	1.1 to 5.0[47-49]
Cardiac $^{13}NH_3$-PET	1.5 to 2.2[49]
CTCA	2.1 to 16[50,51]
MRI	0
Echo	0
Average background dose of radiation per year	1-3.0[52-54]

CTCA = computed tomography coronary angiography; Echo = echocardiography; ^{18}FDG- PET = ^{18}fluorodeoxyglucose-positron emission tomography; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; mSv = millisevert; $^{13}NH_3$ = 13N-labelled ammonia; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technitium-99m; ^{201}Tl =Thallium-201.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to detect ischemia are presented by imaging modality. A summary of the availability of personnel required to detect ischemia, by SPECT or any of the alternative imaging modalities, is provided in Table 5.

^{99m}Tc-labelled radiotracer SPECT MPI

In Canada, physicians involved in the performance, supervision, and interpretation of cardiac nuclear imaging (specifically MPI using ^{99m}Tc-labelled radiotracer) should be nuclear medicine physicians with particular expertise in nuclear cardiology (nuclear cardiologists). Cardiologists also provide much of the nuclear cardiology services. According to the Canadian Medical Association (CMA), there are 1,149 practising cardiologists in Canada (CMA, 2011).

Nuclear medicine technologists are required to conduct MPI. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

All alternative imaging modalities

In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound should be diagnostic radiologists[55] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[73] According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011).

Medical radiation technologists (MRTs) must be certified by the CAMRT, or an equivalent licensing body. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted-part time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[73]

CTCA
CTCA is a CT-based test. Cardiologists provide much of the CTCA service. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011).

For the performance of CT scan, medical radiation technologists who are certified by the CAMRT, or an equivalent licensing body recognized by the CAMRT, are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

Stress Echo
Echo is a U/S based test. Cardiologists provide much of the Echo service. A 2002 report by the CCS reported that 43% of cardiologists do Echo. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). It is assumed that less than 500 of them do Echo.

Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[55] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[55] A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Stress MRI
Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Stress PET
In Canada, physicians involved in stress PET scanning should be nuclear medicine physicians, nuclear cardiologists, or cardiologists with training and expertise in nuclear imaging. In Canada, physicians who perform PET imaging studies must be certified by either the Royal College of Physicians and Surgeons of Canada or le Collège des médecins du Quebec.

Technologists must be certified by CAMRT or an equivalent licensing body. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Table 5: Medical Imaging Professionals in Canada, 2007[55]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**MRTs**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRT = medical radiation technologist; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; ON = Ontario; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 6 provides an overview of the availability of equipment required to detect ischemia. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010. Data were not available for Echo.

Table 6: Diagnostic Imaging Equipment in Canada[55,56,58]				
	Nuclear Medicine Cameras	**CT Scanners**	**MRI Scanners**	**PET or PET/CT**
Number of devices	603[55]	460[56]	218[56]	36[58]
Average number of hours of operation per week (2006-2007)	40	60	71	NA
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	NL, PEI, SK, YT, NT, NU

CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; NB = New Brunswick; NL. = Newfoundland; NS = Nova Scotia; NU = Nunavut; NT = Northwest Territories; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon.

^{99m}Tc-labelled radiotracer SPECT
Nuclear medicine facilities with gamma cameras are required for SPECT imaging. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[55]

CT
No CT scanners are available in Nunavut.[56] The average weekly use of CT scanners ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[55] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[57] The average wait time for CTCA was not reported.

Echo
No information was found to identify how many Echo machines are available in Canada.

MRI
No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[56] According to the Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[55] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[57]

PET
A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[58] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[58] There are 36 PET or PET/CT scanners in Canada, four of which are used for research purposes only.[58]

Wait times
Wait time benchmarks for cardiac nuclear imaging set by the Wait Time Alliance[38] are immediate to 24 hours for emergency cases (immediate danger to life, limb, or organ); within three days for urgent cases (situation that is unstable and has the potential to deteriorate quickly and result in an emergency admission); and within 14 days for scheduled cases (situation involving minimal pain, dysfunction, or disability — routine or elective).

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of SPECT MPI and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 7), the cost of MPI with ^{99m}Tc-based radioisotopes is $964.53. The cost of MPI with ^{201}TI or with PET is assumed to be greater than imaging with ^{99m}Tc-based radioisotopes. Stress MRI is minimally less costly than MPI with ^{99m}Tc. CTCA and stress Echo are moderately less costly.

Table 7: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[74]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
^{99m}Tc-SPECT MPI				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)	44.60	31.10	75.7
J813	Studies with ejection fraction	138.60	82.25	220.85
J807	Myocardial perfusion scintigraphy — resting, immediate post-stress	223.15	50.15	273.3
J808	MPI — delayed	82.15	27.45	109.6
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole-thallium stress test	52.05	75.00	127.05
Maintenance fees — from global budget		50.78		50.78
	TOTAL	635.93	328.6	**964.53**
^{201}Tl-SPECT MPI				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)	44.60	31.10	75.7
J813	Studies with ejection fraction	138.60	82.25	220.85
J807	Myocardial perfusion scintigraphy — resting, immediate post stress	223.15	50.15	273.3
J808	MPI — delayed	82.15	27.45	109.6
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole-thallium stress test	52.05	75.00	127.05
Maintenance fees — from global budget		50.78		50.78
	TOTAL	635.93	328.6	**964.53**
CTCA				
X235	Cardiothoracic CT		155.25	155.25
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		50.78		50.78
	TOTAL	350.78	155.25	**506.03**
Stress Echo				
G570/G571	Complete study — 1 and 2 dimensions	76.45	74.10	150.55
G577/G578	Cardiac Doppler study, with or without colour Doppler, in conjunction with complete 1 and 2 dimension Echo studies	45.15	36.90	82.05
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole-thallium stress test	52.05	75.00	127.05
	TOTAL	218.25	248.65	**466.90**
Stress MRI				
X441C	MRI — thorax — multislice sequence		77.20	77.20
X445C (×3)	Repeat (another plane, different pulse		38.65 (×3)	115.95

	sequence — to a maximum of 3 repeats)		= 115.95	

Table 7: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[74]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
X499C	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40
G315/G319	Maximal stress ECG	44.60	62.65	107.25
X486C	When cardiac gating is performed (must include application of chest electrodes and ECG interpretation), add 30%		96.36	96.36
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	417.60	417.56	**835.16**
Stress PET				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)		31.10	31.10
J813	Studies with ejection fraction		82.25	82.25
J807	Myocardial perfusion scintigraphy — resting, immediate post-stress		50.15	50.15
J808	MPI — delayed		27.45	27.45
G315/G319	Maximal stress ECG		62.65	62.65
G111/G112	Dipyridamole-thallium stress test		75.00	75.00
Technical cost — from global budget		800.00		800.00
	TOTAL	800.00	328.60	**1128.60**

3-D = three-dimensional; CT = computed tomography; CTCA = computed tomography coronary angiography; ECG = electrocardiogram; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; PET = positron emission tomography; Prof. = professional; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m; ^{201}Tl = thallium-201; tech. = technical.

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Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Clinical Uses	
Criterion	**Definition**
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to March 29, 2011>
Date of Search:	March 29, 2011
Alerts:	Monthly search updates began March 29, 2011 and ran until October 2011.
Study Types:	Health technology assessments; systematic reviews; meta-analyses; diagnostic accuracy studies
Limits:	English language Publication years 2006-2011 for diagnostic studies search; no date limits for systematic review search. Diagnostic accuracy studies search limited to human population

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search; includes title, abstract, name of substance word, subject heading word, and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names

Multi-database Strategy	
#	**Searches**
1	exp Myocardial Ischemia/
2	((Myocardial or cardiac or heart or coronary) adj5 (ischemia* or ischemic or ischaemia* or ischaemic)).ti,ab.
3	(Coronary artery disease* or Coronary Arteriosclerosis or Coronary Atherosclerosis or atherosclerotic heart disease* or coronary heart disease* or coronary disease*).ti,ab.
4	or/1-3
5	Technetium/
6	exp Technetium Compounds/
7	exp Organotechnetium Compounds/
8	exp Radiopharmaceuticals/

9	(Technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc*).tw,nm.
10	Radionuclide Imaging/ or Perfusion Imaging/
11	radionuclide imaging.fs.
12	radioisotope*.mp.
13	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
14	exp Tomography, Emission-Computed, Single-Photon/
15	(single-photon adj2 emission*).ti,ab.
16	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
17	Myocardial Perfusion Imaging/
18	(myocardial perfusion imag* or 99MTC-SPECT or rest-stress test* or cardiac-stress test*).ti,ab.
19	(sestamibi or Hexamibi or Tc MIBI or Cardiolite* or tetrofosmin* or myoview*).ti,ab.
20	(109581-73-9 or 112144-90-8 or 113720-90-4).rn.
21	or/5-20
22	meta-analysis.pt.
23	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
24	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
25	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
26	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
27	(data synthes* or data extraction* or data abstraction*).ti,ab.
28	(handsearch* or hand search*).ti,ab.
29	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
30	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
31	(meta regression* or metaregression* or mega regression*).ti,ab.
32	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
33	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
34	(cochrane or health technology assessment or evidence report).jw.
35	or/22-34
36	4 and 21 and 35
37	limit 36 to english language
38	exp "Sensitivity and Specificity"/
39	Diagnostic Errors/
40	False Positive Reactions/
41	False Negative Reactions/
42	(sensitivit* or specificit* or distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti.
43	(predictive adj4 value*).ti,ab.
44	Validation Studies.pt.
45	or/38-44
46	4 and 21 and 45
47	46 not case reports.pt.
48	exp animals/

49	exp animal experimentation/
50	exp models animal/
51	exp animal experiment/
52	exp vertebrate/
53	or/48-52
54	exp humans/
55	53 not 54
56	47 not 55
57	56
58	limit 57 to (english language and yr="2006 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library (Issue 3, 2011)	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 16-22, 2011
Keywords:	Included terms for myocardial ischemia, coronary artery disease, and radionuclide imaging
Limits:	English language

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Position or Consensus Statements

In 2011, the European Association of Nuclear Medicine (EANM), the European Society of Cardiac Radiology (ESCR), and the European Council of Nuclear Cardiology (ECNC) released a joint position statement on use of hybrid cardiac imaging with single-photon emission computer tomography (SPECT) or positron emission tomography (PET) combined with computed tomography (CT) — (SPECT/CT, PET/CT) — to image anatomical and physiologic cardiac abnormalities in a single setting.[66] A review of the literature demonstrated that hybrid SPECT/CT and PET/CT imaging provides superior information compared with either stand-alone or side-by-side interpretation of patients with known or suspected coronary artery disease (CAD). Hybrid cardiac imaging has the advantage of being non-invasive and offering patient-friendly image acquisition in only one visit to the imaging department. Additionally, fewer personnel are required compared with two stand-alone scanners. Disadvantages include proper patient selection to ensure optimal diagnostic effectiveness and minimization of costs, and radiation dose (ranging between 1 and 20 millisievert [mSv]).

A 2007 position statement published by the Canadian Cardiovascular Society (CCS), the Canadian Association of Radiologists (CAR), the Canadian Association of Nuclear Medicine (CANM), and the Canadian Society of Cardiac Magnetic Resonance (CanSCMR) systematically reviewed the available scientific literature on cardiac imaging using PET, MRI, and multidetector computed tomographic angiography (MD-CTA) in the diagnosis and evaluation of ischemic heart disease.[65] The systematic review included literature on any of the three imaging modalities, for one or more of the following outcomes: diagnostic accuracy for the detection of CAD, CAD prognostication, myocardial viability detection, and viability prognostication.[65] Three-thousand six-hundred and fifty-five references were identified in the initial search.[65] Meta-analysis of 14 primary studies on the use of PET for detection of CAD produced sensitivity and specificity estimates of 89% (83% to 100%) and 89% (73% to 100%).[65] One systematic review and eight primary studies on the use of PET in the diagnosis of myocardial viability were included in the review, and provided sensitivity and specificity estimates of 91% (80% to 100%) and 61% (44% to 92%).[65] Nineteen primary studies were pooled to provide estimated sensitivity (87%) and specificity (96%) values for the ability of 16-slice multidetector computed tomography to define angiographic disease. Four studies described the detection of disease in patients using 64-slice multidetector computed tomography to be both sensitive (91%) and specific (95%).[65] Eight studies were used in the calculation of sensitivity (90%) and specificity (84%) of stress wall motion magnetic resonance imaging (MRI).[65] Eleven studies showed the average sensitivity and specificity of stress perfusion MRI to be 84% and 86%, respectively.[65] Finally, with late Gd enhancement, the sensitivity and specificity of MRI for predicting recovery of left ventricular function were estimated to be 81% and 83% (based on 13 studies).[65] This evidence was combined with clinical expertise and opinion to determine the CCS/CAR/CANM/CanSCMR recommendations.[65]

Appendix 4: Comparative Diagnostic Accuracy

Diagnostic Accuracy Reported in MAS Review on the Use of Non-invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease[13-17]									
Test	**Reference Standard**	**Indication**	**Report**	**Period Reviewed**	**No. of Trials (patients)**	**Pooled Sensitivity (%) (95% CI)**	**Pooled Specificity (%) (95% CI)**	**DOR**	**AUC**
^{99m}Tc - SPECT	Coronary angiography	Diagnosis of CAD	No. 8[17]	Jan. 1, 2004 – Aug. 22, 2009	39 (3,488)	88 (85-91)	70 (64-76)	16.80 (10.88-22.71)	NR
^{201}Tl-SPECT					24 (3,338)	84 (80-88)	71 (64-78)	12.88 (7.58-18.18)	NR
Stress Echo	Coronary angiography	Diagnosis of CAD	No. 9[14]	Jan. 1, 2004 – Aug. 22, 2009	127* (13,035)	80 (77-82)	84 (82-87)	20.64 (16.63-24.64)	0.895
Contrast Echo	Coronary angiography	Diagnosis of CAD in patients with suspected CAD	No.10[13]	Jan. 1, 2004 – June 30, 2009	10	87.3 (83.2-90.8)	86.0 (82.0-89.4)	NR	0.944
		Diagnosis of CAD in patients with suspected or known CAD			12 (6 MPA and 6 WMA)	MPA: 87.8 (83.5-89.9)	MPA: 64.9 (59.1-70.4)	NR	MPA: 0.865
						WMA: 69.2 (64.8-73.4)	WMA: 79.4 (72.3-85.4)		WMA: 0.867
64-slice CTA	Coronary angiography	Diagnosis of CAD	No. 11[14]	Jan. 1, 2004 – June 20, 2009	8	97.7 (95.5-99.9)	78.8 (70.8-86.8)	NR	0.9435
					OMCAS trial (117 patients)	81.2 (71.9-89.6)	95.8 (85.7-99.5)	NR	NR
					8 studies + OMCAS trial	96.1 (94.0-98.3)	81.5 (73.0-89.9)	108.60 (30.22-186.97)	0.9622

Diagnostic Accuracy Reported in MAS Review on the Use of Non-invasive Cardiac Imaging Technologies for the Diagnosis of Coronary Artery Disease[13-17]									
Test	**Reference Standard**	**Indication**	**Report**	**Period Reviewed**	**No. of Trials (patients)**	**Pooled Sensitivity (%) (95% CI)**	**Pooled Specificity (%) (95% CI)**	**DOR**	**AUC**
Stress MRI	Coronary angiography	Diagnosis of CAD	No. 12[15]	Jan. 1, 2005 – Oct. 9, 2008	One MA + 11 studies	MPA: 91 (89-92)	MPA: 81 (77-85)	MPA: 37.91	MPA: 0.930
						WMA: 83 (79-88)	WMA: 86 (81-91)	WMA: 26.27	WMA: 0.926

AUC = area under the curve; CAD = coronary artery disease; CI = confidence interval; CTA = computed tomographic angiography; DOR = diagnostic odds ratio; echo = echocardiography; MA = meta-analysis; MAS = Medical Advisory Secretariat; MPA = myocardial perfusion analyses; MRI = magnetic resonance imaging; NR = not reported; OMCAS = Ontario Multidetector Coronary Angiography Study; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m; ^{201}Tl = thallium-201; WMA = wall motion analyses.

* A study was counted twice if data were reported on different stress agents.

Relative Diagnostic Accuracy of Computed Tomography, using ^{99m}Tc-SPECT as a Reference Standard[23-25]										
Study Details		**Population**			**Outcome**					
Author	**Publication Date**	**N**	**Mean Age**	**Patient Characteristics**	**Reference Standard**	**Sens. (%)**	**Spec. (%)**	**Acc. (%)**	**PPV (%)**	**NPV (%)**
Cheng[23]	2010	55	60.7	Patients with known or suspected CAD	Rest SPECT	100	78.0	83.6	60.9	100
					Stress SPECT	83.3	90.3	87.3	87.0	87.5
Bauer[24]	2009	73	56	Patients with known or suspected CAD	Any perfusion defect (^{99m}Tc-SPECT)	46	83	NR	58	75
					Reversible perfusion defect (^{99m}Tc-SPECT)	33	83	NR	33	83
Ruzsics[25]	2009	37	57	Patients with known or suspected CAD with pre-test probabilities of low (22%), intermediate (63%) and high (15%)	All perfusion defects (^{99m}Tc-SPECT)	97	67	92	93	80
					Fixed perfusion defects (^{99m}Tc-SPECT)	94	67	87	89	80
					Reversible perfusion defects (^{99m}Tc-SPECT)	100	67	89	87	100

Acc = accuracy; CAD = coronary artery disease; NPV = negative predictive value; PPV = positive predictive value; Sens. = sensitivity; Spec. = specificity; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m.

Appendix 5: Definitions

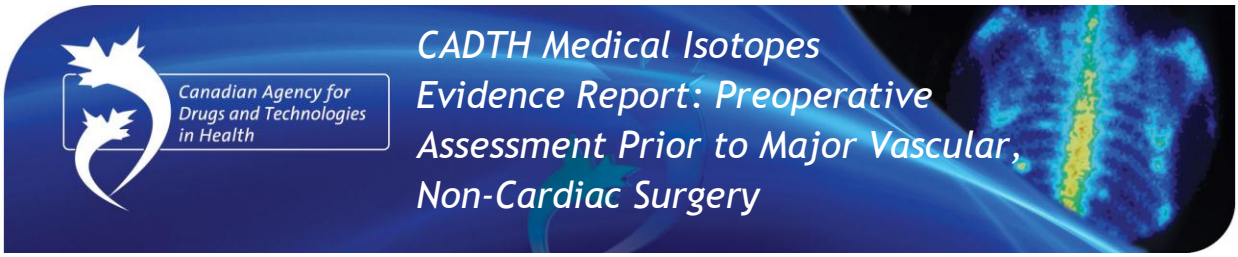
Angina (*angina pectoris*): severe pain and constriction around the heart.[75]

Ischemia: insufficient blood supply to the heart muscle due to obstruction.[75]

Myocardium: the middle layer of the walls of the heart, composed of cardiac muscle.[75]

Stenosis (stenosis cardiac): A narrowing or constriction of any of the orifices leading into or from the heart, or between the chambers of the heart.[75]

APPENDIX 2.9



INDICATION OVERVIEW

Many patients undergoing major vascular surgery to manage diseases of the aorta and peripheral arteries are at risk for cardiovascular complications during or following the vascular surgery.[1] Cardiac complications after non-cardiac surgery depend on specific risk factors, the type of surgery, and the circumstances under which the surgery takes place.[2] The major predictors of risk include recent myocardial infarction (MI), severe angina, recent percutaneous coronary intervention, significant arrhythmias, elevated plasma brain natriuretic peptide, diabetes, renal insufficiency, cerebrovascular disease, and obesity.[1] The *American College of Cardiology/American Heart Association (ACC/AHA) 2007 Guidelines on Perioperative Cardiovascular Evaluation and Care for Noncardiac Surgery*[3] stratify cardiac risk of non-cardiac surgery, according to procedure — vascular surgery is associated with the highest cardiac risk. As such, patients undergoing major non-cardiac vascular surgery should undergo a complete clinical assessment of comorbidities.[4] Because of the high prevalence of symptomatic and asymptomatic coronary artery disease (CAD) in this patient population, the clinical assessment aims to identify patients at increased risk of cardiac complications and apply strategies to reduce this risk.[5,6]

Population: Patients undergoing major high-risk vascular non-cardiac surgery (including aortic and peripheral vascular surgery). Patients undergoing major non-vascular surgeries may also be at risk for cardiac complications; however, the document search for this report was focused on major, high-risk vascular surgery. In some instances, the findings may be generalizable to situations of major non-vascular surgery.

Intervention: Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) with technetium-99m (^{99m}Tc)-labelled radiotracers.

As with nuclear imaging for other cardiac indications, the relative distribution of the radionuclide allows for visualization of blood flow through the heart and gives information regarding the functional capacity of the heart.

This identifies patients at greater risk for cardiac complications following surgery so that appropriate testing and therapeutic measures can be taken.[1] The basic principle of radionuclide MPI is to administer a radiopharmaceutical intravenously and image blood flow to the heart muscle (myocardial perfusion), both at rest and under stress. Stress is induced by either exercise or a pharmaceutical agent (dobutamine, dipyridamole, or adenosine), which increases coronary blood flow to the myocardium.[7] Viable myocardial cells take up the radionuclide tracer (either thallium isotope [^{201}Tl] or isotope ^{99m}Tc-labelled radiotracer) in proportion to blood flow.[7,8] Through sequential image acquisition, the gamma camera works with a computer to evaluate cardiac function and perfusion.[9]

Comparators: For this report, the following diagnostic tests are considered as alternatives to stress MPI with the ^{99m}Tc:

- *Computed tomography (CT) angiography (CTA, computed tomography coronary angiogram [CTCA], cardiac CT)*
- *Stress SPECT MPI (using ^{201}TI)*
- *Stress echocardiography (Echo) (also called pharmacologic [dobutamine, dipyridamole, or adenosine] echocardiography)*
- *Stress magnetic resonance imaging (MRI)*
- *Stress positron emission tomography (PET) (using rubidium-82 [Rb-82] or 13N-labelled ammonia [$^{13}NH_3$]).*

Preoperative non-invasive testing aims to provide information primarily about coronary artery disease (myocardial ischemia or reduced blood supply to the heart muscle), left ventricular (LV) dysfunction, and heart valve abnormalities in selected patients.[2] None of the tests are perfect and some are contraindicated in certain patient populations or clinical situations. Exercise stress tests are often not feasible in patients with peripheral arterial disease (PAD) due, in part, to baseline abnormalities on the resting echocardiogram (ECG).[10]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 3) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and non-cardiac surgery, combined with pre-operative assessment or operative complications.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2001 and March 7, 2011. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

There were 11 articles identified through the meta-analyses/systematic review/health technology assessment (MA/SR/HTA) search. Seven were subjected to full-text review, and two were ultimately included.[5,11] Three reviews — published in 1994,[6] 1996,[12] and 1999[13] — were excluded, as they were outdated and did not include SPECT stress MPI with ^{99m}Tc. One review,[14] published in 2002, was excluded, as it did not provide an analysis of relative diagnostic accuracy. An additional publication was excluded as it was a commentary on a systematic review.

Two guidelines of interest were identified in the grey literature search: the ACC/AHA guidelines[3] and the European Society of Cardiology guidelines.[2] The ACC/AHA guidelines[3] include a summary of studies examining the value of MPI for preoperative assessment of cardiac risk, including two studies published after 2001.[15,16] Procedure guidelines adopted by the British Cardiovascular Society, British Nuclear Cardiology Society, and British Nuclear Medicine Society,[17] and a Consensus Document produced by the Canadian Cardiovascular Society[10] were obtained through targeted searching.

Two-hundred and seventy-seven articles were identified in the initial search for primary literature. Thirty-four of these were reviewed in full-text, but none were found to provide estimates of the relative diagnostic accuracy of the various imaging modalities.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	An estimated 1.7/1,000 (0.17%) Canadians undergo high-risk, non-cardiac surgeries each year. Those with intermediate clinical risk predictors or minor risk predictors and poor functional capacity should undergo preoperative cardiac assessment. Assuming that the proportion of surgical patients meeting these criteria is between 10% and 50% of those undergoing high-risk, non-cardiac surgeries, the size of the affected population is assumed to be more than 1 in 10,000 (0.01%) and less than 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	The CCS recommends non-invasive testing in select patients scheduled for elective vascular surgery.[10] The wait time for the elective surgery dictates the timelines and urgency of the preoperative assessment. According to the Wait Time Alliance, the benchmarks for cardiac nuclear imaging are: “immediate to 24 hours” for emergent cases, “within three days” for urgent cases, and “within 14 days” for scheduled cases.[18] While it is understood that the timeliness and urgency of imaging is related to the timeliness and urgency of the surgery, in general, it is assumed that the target time frame for imaging is between eight and 30 days, and obtaining the test results in the appropriate timely manner has significant impact on the management of the condition or the effective use of health care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	The number needed to treat to prevent mortality at one year has been estimated at 221 (95% CI, [confidence interval] 111 to 16,067).[19] For patients undergoing aortic surgery, stress testing with or without coronary revascularization is associated with significantly lower rates of perioperative mortality (3.8% versus 9.0%).[20] Diagnostic imaging test results can have a moderate impact on mortality.

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria related to the Underlying Health Condition		
Criterion		**Synthesized Information**
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Perioperative events that may impact morbidity and quality of life include CHF, unstable angina, and MI. Most studies evaluating the use of SPECT for preoperative evaluation have death, or some combined outcome including death, as their outcome of interest, making it difficult to isolate the impact of not performing the test on patient morbidity or quality of life. It is assumed that diagnostic imaging test results have moderate impact on morbidity or quality of life.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	A 2004 British study (of relatively small sample size) compared patient satisfaction and preference toward SPECT MPI versus MRI and found little difference.[21] Patients rated the two tests similarly on overall preference, duration, comfort, and safety, with a non-significant preference for MRI on all of the above.[21] The only statistically significant finding was that the SPECT scan was preferred in terms of space on the scanner.[21] Patients undergoing computed tomography coronary angiography (CTCA) scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. Stress echocardiography (Echo) may be preferred by some patients, as there is no radiation exposure with it. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[22,23] Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent associated with stress PET imaging. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

SPECT stress MPI with ^{99m}Tc-labelled radiotracers:
• is minimally less acceptable to patients than CTCA
• is minimally less acceptable to patients than stress Echo
• has similar patient acceptability as stress MRI
• is minimally less acceptable to patients than stress PET
• has similar patient acceptability as stress SPECT with ^{201}TI-labelled radiotracers.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>Kertai et al.[5] meta-analyzed the prognostic accuracy of six diagnostic tests: radionuclide ventriculography, ambulatory Echo, exercise electrocardiography, MPS, dobutamine stress Echo, and dipyridamole stress Echo. Dobutamine stress Echo showed the highest sensitivity (true positive ratio) to detect cardiac risk of the six tests included in the analysis. The sensitivity of MPS was also found to be high (83% versus 85% with dobutamine stress Echo), but the specificity was lower than dobutamine stress Echo (49% versus 70% with dobutamine stress Echo). Based on the results, the authors concluded the dobutamine stress Echo showed a trend toward better diagnostic performance than the other tests. It should be noted that this systematic review used published reports from January 1975 to April 2001 and that imaging technology has improved significantly in all areas.

<table>
<tr><th colspan="3">Diagnostic Accuracy</th></tr>
<tr><th>Test</th><th>Sensitivity, %
(95% CI)</th><th>Specificity, %
(95% CI)</th></tr>
<tr><td>MPS</td><td>83 (77 to 89)</td><td>49 (41 to 57)</td></tr>
<tr><td>Dobutamine stress Echo</td><td>85 (74 to 97)</td><td>70 (62 to 79)</td></tr>
<tr><td>Dipyridamole stress Echo</td><td>74 (53 to 94)</td><td>86 (80 to 93)</td></tr>
</table>
CI = confidence interval; Echo = echocardiography; MPS = myocardial perfusion scintigraphy.
No estimates were identified for the diagnostic accuracy of CTCA, PET, or stress MRI in the</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		preoperative assessment of patients undergoing major vascular, non-cardiac surgery. Based on the limited evidence available to inform this criterion, it is assumed that the diagnostic accuracy of SPECT MPI with ^{99m}Tc-labelled radiotracers is: • minimally better than CTCA • similar to stress Echo • minimally lower than stress MRI • minimally lower than stress PET • minimally better than SPECT MPI with ^{201}TI-labelled radiotracers.
8	**Relative risks associated with the test**	**Non–radiation-related risks** The main risks of non-invasive preoperative assessment relate to the stress component of the tests (stress SPECT MPI, stress Echo, stress MRI, and stress PET. With exercise stress testing, there is a small risk of patients sustaining an MI if they have significant CAD.[24] With dipyridamole stress testing, there are multiple potential side effects, including headache, exacerbated asthma, and heart attack (risk of this event is low).[24] With adenosine stress testing, side effects similar to dipyridamole may be experienced. Symptoms of chest pain or pressure may also occur, but these side effects go away quickly once the adenosine administration stops.[24] With dobutamine stress testing, some patients may experience light-headedness and nausea. There is a theoretical risk of inducing a fast and abnormal cardiac rhythm (i.e., atrial fibrillation, ventricular tachycardia, ventricular fibrillation); however, this is unlikely with the doses of dobutamine used. A slight risk of MI exists.[24] The overall risk of sustaining a heart attack from a stress test is estimated to be about 2 to 4 in 10,000.[24] Apart from risks associated with stress testing, a review of undesirable events with radiopharmaceuticals reported anaphylactic reactions and erythmea multiforme (i.e., a type of skin reaction) with sestamibi, although these reactions may be rare.[25] With CTCA, some patients may experience an allergic reaction or side effect from the contrast agent. The frequency of severe, life-threatening reactions with the agent gadolinium (Gd) are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions are also rare (0.004% to 0.7%).[26] The risks associated with stress testing would not apply for cardiac imaging using CTCA. Apart from risks associated with stress testing, there is a low risk of adverse events associated with

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		the contrast agent used in stress Echo imaging. Apart from risks associated with stress testing, MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[27] Side effects of Gd include headaches, nausea, and metallic taste. The frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions are also rare (0.004% to 0.7%)[26] Apart from risks associated with stress testing, the Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[28] **Radiation-related Risks** Among the modalities to assess patients prior to major vascular, non-cardiac surgery, ^{99m}Tc-SPECT MPI, ^{201}Tl-SPECT MPI, CTCA, and PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in the subsequent table:

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th colspan="2">Effective Doses of Radiation</th></tr>
<tr><th>Procedure</th><th>Average Effective Dose (mSv)</th></tr>
<tr><td>^{99m}Tc-SPECT MPI</td><td>7 to 12.8[29]</td></tr>
<tr><td>^{201}Tl-SPECT MPI</td><td>17 to 41[29,30]</td></tr>
<tr><td>Cardiac ^{18}FDG-PET</td><td>7(MIIMAC expert opinion) to 14[30]</td></tr>
<tr><td>Cardiac ^{82}Rb-PET</td><td>1.1 to 5.0[30-32]</td></tr>
<tr><td>Cardiac $^{13}NH_3$-PET</td><td>1.5 to 2.2[32]</td></tr>
<tr><td>CTCA</td><td>2.1 to 16[33,34]</td></tr>
<tr><td>Stress MRI</td><td>0</td></tr>
<tr><td>Stress Echo</td><td>0</td></tr>
<tr><td>Average background dose of radiation per year</td><td>1-3.0[35-37]</td></tr>
</table>
CTCA = computed tomography coronary angiography; Echo = echocardiogram; ^{18}FDG =18F-fluorodeoxyglucose; MIIMAC = Medical Isotopes and Imaging Modalities Advisory Committee; MRI = magnetic resonance imaging; mSv = millisievert;$^{13}NH_3$ = 13N-labelled ammonia; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technitium-99m; ^{201}Tl = thallium-201.

Overall, ^{99m}Tc-SPECT MPI:
• and CTCA have similar safety profiles
• and stress Echo have similar safety profiles
• and stress MRI have similar safety profiles
• and stress PET have similar safety profiles
• and ^{201}Tl-SPECT have similar safety profiles.
</td></tr>
<tr><td>**9**</td><td>**Relative availability of personnel with expertise and experience required for the test**</td><td>In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic nuclear imaging, CT scans, MRI, and U/S should be diagnostic radiologists or nuclear medical physicians. According to the CMA, there are 1,149 practicing cardiologists in Canada.[38] Not all radiologists, nuclear medical physicians, nuclear cardiologists, or cardiologists have the expertise to conduct ^{99m}Tc-SPECT and all of its alternatives. For example, a 2002 report by the CCS reported that 43% of cardiologists do Echo.

Assuming the necessary equipment is available, if ^{99m}Tc-SPECT imaging is not available it is assumed that:</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		• 25% to 74% of the procedures can be performed in a timely manner using CTCA • 25% to 74% of the procedures can be performed in a timely manner using Echo • fewer than 25% of the procedures can be performed in a timely manner using MRI • 25% to 74% of the procedures can be performed in a timely manner using PET • more than 95% of the procedures can be performed in a timely manner using ^{201}TI-SPECT.
10	**Accessibility of alternative tests (equipment and wait times)**	For SPECT MPI, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the YT, NT, or NU.[39] A report from the CIHI states that, as of January 1, 2007, CT scanners were available at a rate of 12.8 per million people in Canada; however, there were none available in NU.[39] For CT scanners, the average weekly use ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[39] In 2010, the average wait time for a CT scan in Canada was 4.2 weeks.[40] As of January 1, 2007, there were 6.8 MRI devices per million population in Canada, with no MRI scanners available in YT, NT, or NU.[39] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[39] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[40] U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[40] Assuming the necessary personnel is available, if ^{99m}Tc-SPECT imaging is not available it is assumed that: • 25% to 74% of the procedures can be performed in a timely manner using CTCA • 75% to 94% of the procedures can be performed in a timely manner using Echo • fewer than 25% of the procedures can be performed in a timely manner using MRI • fewer than 25% of the procedures can be performed in a timely manner using PET • more than 95% of the procedures can be performed in a timely manner using ^{201}TI-SPECT.
11	**Relative cost of the test**	According to our estimates, the cost of MPI with ^{99m}Tc-based radioisotopes is $964.53. The cost of MPI with ^{201}TI or with PET is assumed to be greater than imaging with ^{99m}Tc-based radioisotopes.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses	
Criterion	**Synthesized Information**
	Stress MRI is minimally less costly than MPI with ^{99m}Tc. CTCA and stress Echo are moderately less costly.

Relative Costs

Test	Total Costs ($)	Cost of Test Relative to ^{99m}Tc-based Test ($)
^{99m}Tc-SPECT MPI	964.53	Reference
^{201}TI-SPECT MPI	964.53	+0.00
CTCA	506.03	–458.50
Stress echo	466.90	–497.63
Stress MRI	835.16	–129.37
Stress PET	1128.60	+164.07

CAD = coronary aretery disease; CCS = Canadian Cardiovascular Society; CHF = congestive heart failure; CI = confidence interval; CIHI = Canadian Institute for Health Information; CT = computed tomography; CTCA = computed tomography coronary angiography; Echo = echocardiography; Gd = gadolinium; MI = myocardial infarction; MPI = myocardial perfusion imaging; MPS = myocardial perfusion scintigraphy; MRI = magnetic resonance imaging; mSv = millisevert; NU = Nunavut; NT = Northwest Territories; PEI = Prince Edward Island; PET = positron emission tomography; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m; ^{201}TI = thallium-201; U/S = ultrasound; YT = Yukon.

CRITERION 1: Size of affected population (link to definition)

CCS estimates that nearly 500,000 Canadians undergo non-cardiac surgery each year; however, only a subset of these patients require preoperative risk assessment.[10] Preoperative non-invasive risk assessment is recommended in patients undergoing intermediate risk or vascular surgery with a low (< 4 metabolic equivalents of task [METs]) or unknown functional capacity and 1 or more clinical risk factors (ischemic heart disease, compensated or prior heart failure, diabetes mellitus, renal insufficiency, cerebrovascular disease) if testing may change management.[10] In emergent cases, or in elective cases in which the patient has had revascularization or a favourable result on a coronary evaluation in the past two to five years, and has been asymptomatic since, no testing is required.[10] Similarly, patients with the functional capacity to walk more than one to two blocks and no risk predictors can proceed directly to operation without preoperative assessment.[10]

Targeted literature searches were conducted in order to estimate the size of the population undergoing high-risk non-cardiac surgical procedures in Canada on an annual basis. Table 2 shows estimated numbers of major vascular procedures performed in Canada annually.

Table 2: Major Vascular Procedures Performed in Canada Annually

Procedure	Number Performed in Canada Per Year
Aortic Repair	
AAA repair	Overall, 2,948 AAA procedures (open repair and EVAR) were performed in nine provinces across Canada in 2008 (data for Quebec are not included),[41] with an estimated prevalence of 1.2/10,000 (0.012%).
Peripheral Vascular Surgery	
CEA (used to prevent stroke, by correcting stenosis or narrowing in the common carotid artery)	Approximately 5,500 CEA procedures were reported during a one-year period (2000–2001),[42] with an estimated prevalence of 1.79/10,000 (0.0179%).
Peripheral vascular bypass (also known as a lower extremity bypass): rerouting of blood flow around an obstructed artery that supplies blood to the legs and feet	126 per 100,000 in the US in 2006,[43] with an estimated prevalence of 1.26/1,000 (0.126%).
Lower extremity amputation	503 in Alberta in 2007,[44] with an estimated prevalence of 1.43/10,000 (0.0143%).
TOTAL	**Estimated prevalence of 1.7/1,000 (0.17%)**

AAA = abdominal aortic aneurysm; CEA = carotid endarterectomy; EVAR = endovascular aneurysm repair.

No literature indicating the proportion of these vascular surgeries for which preoperative risk assessment is indicated was identified.

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

In the case of emergency surgical procedures, such as those for a ruptured abdominal aortic aneurysm (AAA) or major trauma, cardiac evaluation will not change the course of the surgical intervention, but may influence the immediate post-operative patient management strategy.[2] In the case of elective surgeries, the results of the preoperative assessment may influence the choice of intervention, or the decision as to whether to intervene at all.[2] For this reason, CCS only recommends non-invasive testing in select patients scheduled for elective vascular surgery.[10] The wait time for the elective surgery may dictate the urgency of the preoperative assessment. For example, the greatest benefit of carotid endarterectomy (CEA) for preventing recurrent stroke is when surgery is performed within two weeks after ischemic stroke or transient ischemic attack.[45] Results from the Registry of the Canadian Stroke Network indicate that the benefit of CEA is reduced when surgery is delayed more than two weeks and essentially lost if delayed more than three months.[45] According to the Wait Time Alliance, the benchmarks for cardiac nuclear imaging are: "immediate to 24 hours" for emergent cases, "within three days" for urgent cases, and "within 14 days" for scheduled cases.[18]

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Failure to perform a preoperative assessment prior to non-cardiovascular surgery may influence patient mortality, as demonstrated by three retrospective analyses.

An Ontario-based study published in 2011[46] evaluated the post-operative survival of patients over the age of 40 years undergoing elective intermediate to high-risk non-cardiac surgery (April 1, 1999 to March 31, 2008). The study cohort consisted of 264,823 patients, 40,084 of whom underwent Echo testing within the six months prior to surgery.[46] Eighty-nine percent (n = 35,498) of the Echo patients were matched to no Echo controls, creating a matched cohort of 70,996 patients. Within the matched cohort, preoperative Echo was associated with a small, statistically significant increase in post-operative mortality (relative risk [RR] = 1.14 at 30 days, RR = 1.07 at one year).[46] The authors concluded that the practice of conducting preoperative Echo may not improve patient mortality.[46]

A previous analysis by the same group of authors investigated the impact of non-invasive cardiac stress testing before elective intermediate- to high-risk non-cardiac surgery on mortality.[19] Patients (n = 23,060) over the age of 40 who underwent stress testing prior to surgery were retrospectively matched with patients who did not undergo stress testing (including graded exercise treadmill testing, nuclear perfusion imaging, and stress Echo). Patients who underwent testing were typically male, and testing was more likely to be conducted at a high- or moderate-volume teaching hospital. Mortality data was collected using the Canadian Institute for Health Information discharge abstract database (in-hospital death) and the Registered Persons Database (out-of-hospital deaths). Within the matched cohort, one year survival was higher among patients who had undergone preoperative testing than in those who had not (hazard ratio [HR] = 0.92, 95% confidence interval [CI], 0.86 to 0.99). Of the patients who underwent stress testing, 914 (3.8%) underwent coronary angiography, 149 (0.6%) underwent percutaneous coronary intervention, and 134 underwent coronary artery bypass graft surgery between the dates of the stress testing and the surgery. The number needed to treat to prevent mortality at one year was calculated to be 221 (95% CI, 111 to 16,067). This number represents

the average number of patients who need to be imaged in order to prevent one death. It is calculated by taking the inverse of the absolute risk reduction.

In 1999, Fleisher et al.[20] investigated mortality rates following vascular surgery using retrospective cohort analysis. The cohort (n = 6,895) was based on a sample of Medicare patients who underwent major vascular surgery in the first six months of 1991 and the first 11 months of 1992.[20] The six-month period prior to each index case was reviewed in order to determine whether preoperative non-invasive cardiovascular imaging or coronary revascularization was performed. The primary study outcome was death within 30 days of surgery.[20] Forty-two per cent of the cohort underwent aortic surgery and the remaining 58% had peripheral vascular surgery.[20] For patients undergoing aortic surgery, stress testing with or without coronary revascularization was associated with significantly lower rates of perioperative mortality (3.8% versus 9.0%).[20]

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Perioperative events that may impact morbidity and quality of life include congestive heart failure, unstable angina, and MI. Most studies evaluating the use of SPECT for preoperative evaluation have death, or some combined outcome including death, as their outcome of interest, making it difficult to isolate the impact of not performing the test on patient morbidity or quality of life.

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CRITERION 5: Relative impact on health disparities (link to definition)

Disparity concerns have been documented with respect to the following disadvantaged groups.

Diabetic patients
According to a report by Hashimoto et al., perioperative cardiac events are more common among patients with diabetes mellitus (DM) than in non-DM patients (RR: 2.6).[47] The usefulness of SPECT in assessing perioperative cardiac risk in DM patients with cardiac disease undergoing peripheral vascular surgery has been well-described.[47-49] Most recently, Bai et al.[50] evaluated the use of SPECT in the preoperative evaluation of diabetic patients without chest pain. There were a number of limitations associated with this study, including the fact that undergoing SPECT was part of the patient inclusion criteria, which likely inflated the frequency of cardiac events.[50] The authors concluded that DM patients undergoing high-risk operations should be particularly concerned with abnormal SPECT findings.[50]

Elderly patients
While the use of MPI has been extensively evaluated in young and middle-aged patients, there are limited guidelines regarding its application in the elderly.[51] A 2006 study by Bai et al.[52] investigated the increased perioperative cardiac risk in the elderly using a retrospective analysis. The records of 1,570 patients who had undergone dipyridamole stress myocardial perfusion SPECT before non-cardiac surgery were review and divided into four groups:

- aged 75 or more, normal SPECT (Group 1-E) n = 270
- aged less than 75, normal SPECT (Group 1-Y) n = 729

- aged 75 or more, abnormal SPECT (Group 2-E) n = 93
- aged less than 75, abnormal SPECT (Group 2-Y) n = 259.

The rate of cardiac events (cardiac death, non-fatal MI, heart failure, or arrhythmias) in the groups undergoing high-risk surgeries were 4.4% (Group 1-E), 4.2% (Group 1-Y), 26.3% (Group 2-E), and 15.4% (Group 2-Y). The authors concluded that aging itself does not influence perioperative cardiac risk in patients with normal SPECT results. In patients with MI or ischemia documented by SPECT, the likelihood of cardiac events increases with age, independently of other clinical variables.

Obese patients
Investigations of obese patients may be limited by their weight or size. Radiographs and Echo may be of poor quality, while some patients may be too big to undergo imaging techniques such as CT or MRI.[53]

Patients at low-volume hospitals
There is considerable evidence to support the hypothesis that patients undergoing high-risk surgeries at high-volume hospitals have better health outcomes, including lower risk of post-operative death, than do patients at low-volume hospitals.[54-56] In 2003, Urbach et al. collected data on patients undergoing five major surgical procedures in Ontario and analyzed the relationship between patient outcomes and the average annual volume of the hospital in which the procedure took place.[57] The authors concluded that there is evidence that a small number of operative deaths could be prevented by restricting four complex surgical procedures, including AAA, to high-volume hospitals.

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

SPECT MPI
A 2004 British study compared patient satisfaction and preference toward SPECT versus MRI adenosine stress myocardial perfusion scans and found little difference.[58] Forty-one patients who had undergone both SPECT and MRI were sent a retrospective questionnaire within two weeks of scan completion. Thirty-five completed questionnaires were returned. When asked “If the two tests (nuclear heart scan and MRI) could provide the same information, which of the two would you prefer?” 12 patients (34%) stated a preference for MRI, nine (26%) stated a preference for SPECT, and 14 (40%) stated no preference.[58] Patients rated the two tests similarly on overall preference, duration, comfort, and safety, with a non-significant preference for MRI on all of the aforementioned.[58] The only statistically significant finding was that the SPECT scan was preferred in terms of space on the scanner.[58] Three participants (9%) stated that they would not have an MRI again, while two patients (6%) said they would not repeat a SPECT.[58] The study authors recognized that the relatively small sample size may have affected their ability to demonstrate statistically significant preference for one scan over the other.[58] Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Computed Tomography Coronary Angiography (CTCA)
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This may be less of a problem with new CT scanners, if available (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert

opinion). Patients may also be required to hold their breath for a substantial period of time, which is seen as “uncomfortable” and “difficult.”[59]

Stress Echo
This test is likely to be well-tolerated by patients. Echo may be preferred by some patients, as there is no radiation exposure. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Stress MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[22,23] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during a MRI scan, which may be more acceptable to some. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

Stress PET Myocardial Perfusion Imaging (rubidium-82 [^{82}Rb] or 13N-labelled ammonia [^{13}NH3])
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Exercise or pharmacological agents used to induce stress conditions may be unpleasant for some patients.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Systematic Reviews and Meta-analyses

Two systematic reviews and meta-analyses reported on the relative accuracy of stress MPI and its alternatives at predicting perioperative cardiac risk in patients undergoing major vascular surgery. Two reviews, published in 1994[6] and 1996,[12] were excluded, as they were outdated and did not include SPECT stress MPI with ^{99m}Tc. An additional review,[14] published in 2002, was excluded, as it did not provide an analysis of relative diagnostic accuracy. No estimates were identified for the diagnostic accuracy of CTCA, PET, or stress MRI in the preoperative assessment of patients undergoing major vascular, non-cardiac surgery.

Kertai et al. (2003)[5] meta-analyzed the prognostic accuracy of six diagnostic tests: radionuclide ventriculography (with ^{99m}Tc), ambulatory electrocardiography, exercise electrocardiography, myocardial perfusion scintigraphy (including both planar and SPECT, ^{99m}Tc and ^{201}Tl), dobutamine stress Echo, and dipyridamole stress Echo. This systematic review included published reports from January 1975 to April 2001; imaging technology has improved significantly in all areas in the past decade. This study was included in the current report despite the fact that the authors did not provide separate analyses for ^{99m}Tc and ^{201}Tl. It is possible that the sensitivity and specificity of ^{99m}Tc is lower or higher than the pooled value. This study was included based on the limited available information for comparing ^{99m}Tc-based imaging to its comparators; however, the limitations of the study should be noted. The results of the analysis are presented in Table 3. A MEDLINE search for English language articles published between January 1975 and April 2001 was conducted, with additional references obtained from the bibliographies of review articles and original papers. If several studies on the same patient population were identified, the report with the largest sample size was selected. Studies in

which a positive test result led to preoperative coronary revascularization were included in the analysis only if the revascularized patients could be excluded or analyzed separately. Data were extracted by two independent reviewers, with discrepancies resolved by consensus. Fifty-eight studies were included in the meta-analysis. Random effects models were used to calculate weighted sensitivity and specificity from the published results. Dobutamine stress Echo showed the highest sensitivity (true positive ratio) to detect cardiac risk of the six tests included in the analysis. The sensitivity of myocardial perfusion scintigraphy was also high (83% versus 85% with dobutamine stress Echo), but the specificity was a lower than dobutamine stress Echo (49% versus 70% with dobutamine stress Echo). Based on the results, the authors concluded the dobutamine stress Echo showed a trend toward better diagnostic performance than the other tests.

Table 3: Sensitivity and Specificity Values Reported by Kertai et al.[5]

Test	No. of Studies	No. of Patients	No. of Events	Sensitivity, % (95% CI)	Specificity, % (95% CI)
Radionuclide ventriculography	8	532	54	50 (32 to 69)	91 (87 to 96)
Ambulatory electrocardiography	8	893	52	52 (21 to 84)	70 (57 to 83)
Exercise electrocardiography	7	685	25	74 (60 to 88)	69 (60 to 78)
Myocardial perfusion scintigraphy	23	3119	207	83 (77 to 89)	49 (41 to 57)
Dobutamine stress Echo	8	1877	82	85 (74 to 97)	70 (62 to 79)
Dipyridamole stress Echo	4	850	33	74 (53 to 94)	86 (80 to 93)

CI = confidence interval; Echo = echocardiography; No. = number.

Stress Echo versus SPECT with ^{201}T-labelled radiotracers

Beattie et al.[11] conducted a meta-analysis comparing preoperative stress Echo and nuclear scintigraphy imaging, published in 2006. Two searches were conducted in March 7, 2005 using MEDLINE: one for ^{201}TI-imaging and the other for stress Echo. There was no language restriction used. The resulting 111 citations were reviewed by two authors. Sixty-eight studies were included in the meta-analysis: 25 assessing stress Echo and 50 assessing thallium (seven studies were direct comparisons). The likelihood ratio (Sensitivity/[1-Specificity]) was the primary outcome measure in the study. The results of the meta-analysis indicate that a positive stress Echo results in a likelihood ratio twice as predictive as a positive ^{201}TI-imaging (4.09 versus 1.83) for predicting post-operative cardiac events. These results are consistent with the results of the review by Kertai et al: stress Echo has superior negative predictive ability when compared with ^{201}TI-imaging. The authors concluded that stress Echo is superior to ^{201}TI-imaging in predicting post-operative cardiac events.

Primary Studies

Two-hundred and seventy-seven articles were identified in the initial search for primary literature. Thirty-four of these were reviewed in full-text. No estimates of diagnostic accuracy were provided.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related risks

Cardiac stress tests
The main risks of non-invasive preoperative assessment relate to the stress component of the tests:

- With exercise stress testing, there is a small risk of patients sustaining an MI if they have significant coronary artery disease.[24]
- With dipyridamole stress testing, there are multiple potential side effects, including headache, exacerbated asthma, and heart attack (risk of this event is low).[24]
- With adenosine stress testing, side effects similar to dipyridamole may be experienced. Symptoms of chest pain or pressure may also occur, but these side effects go away quickly once the adenosine administration stops.[24]
- With dobutamine stress testing, some patients may experience light-headedness and nausea. There is a theoretical risk of inducing a fast and abnormal cardiac rhythm (i.e., atrial fibrillation, ventricular tachycardia, ventricular fibrillation); however, this is unlikely with the doses of dobutamine used. A slight risk of MI exists.[24]

The overall risk of sustaining a heart attack from a stress test is estimated to be about 2 to 4 in 10,000.[24]

Stress SPECT
Apart from risks associated with stress testing, a review of undesirable events with radiopharmaceuticals reported anaphylactic reactions and erythemea multiforme (i.e., a type of skin reaction) with sestamibi, although these reactions may be rare.[25]

CTCA
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[27] In addition, patients may experience mild side effects such as nausea, vomiting, or hives from the contrast agent. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and gadolinium (Gd) contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found that 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[60] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. Patients must be able to take rate-lowering medications. Although rarely used in cardiac imaging, Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media,*[26] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[26] The risks associated with stress testing would not apply for cardiac imaging using CTCA.

Stress Echo
Apart from risks associated with stress testing, three relatively large studies — with sample sizes of 42,408 patients (2009),[61] 26,774 patients (2009),[62] and 5069 patients (2008)[63] — compared cardiac outcomes (non-fatal MI or death) between patients who underwent contrast-enhanced Echo with patients who had an Echo without contrast. All three studies concluded that

the risk of an adverse event is low and is no different than for patients who received no contrast. No additional risks associated with Echo were identifed.

Stress MRI
Apart from risks associated with stress testing, MRI is contraindicated in patients with metallic implants including pacemakers.[64] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[27] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[26] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[26]

Stress PET myocardial perfusion imaging (^{82}Rb or ^{13}NH3)
Apart from risks associated with stress testing, the Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[28] The risks associated with stress testing would apply for cardiac imaging using PET.

Radiation-related risks

Among the modalities to assess patients prior to major vascular, non-cardiac surgery, ^{99m}Tc-SPECT MPI, ^{201}Tl-SPECT MPI, CTCA, and PET expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 4.

Table 4: Effective Doses of Radiation

Procedure	Average Effective Dose (mSv)
^{99m}Tc-SPECT MPI	7 to 12.8[29]
^{201}Tl-SPECT MPI	17 to 41[29,30]
Cardiac ^{18}FDG-PET	7(MIIMAC expert opinion) to 14[30]
Cardiac ^{82}Rb-PET	1.1 to 5.0[30-32]
Cardiac $^{13}NH_3$-PET	1.5 to 2.2[32]
CTCA	2.1 to 16[33,34]
MRI	0
Echo	0
Average background dose of radiation per year	1-3.0[35-37]

CTCA = computed tomography coronary angiography; Echo = echocardiography; ^{18}FDG- PET = ^{18}fluorodeoxyglucose-positron emission tomography; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; mSv = millisevert; $^{13}NH_3$ = 13N-labelled ammonia; PET = positron emission tomography; ^{82}Rb = rubidium-82; SPECT = single-photon emission computed tomography; ^{99m}Tc = Technitium-99m; ^{201}Tl =Thallium-201.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The patient's primary physician or surgeon may request a cardiology consultation prior to conducting major vascular surgery. According to the ACC/AHA 2007 Perioperative Guidelines, the role of the consultant is to determine the stability of the patient's cardiovascular status.[3] The consultant may recommend changes in medication, preoperative tests or procedures, or higher levels of post-operative care.[3]

The personnel required for the performance of the imaging tests to assess patients undergoing major vascular, non-cardiac surgery are presented by imaging modality. A summary of the availability of personnel required for the conduct of methods to assess patients undergoing major vascular, non-cardiac surgery, by SPECT or any of the alternative imaging modalities, is provided in Table 5.

^{99m}Tc-labelled radiotracer SPECT MPI

In Canada, physicians involved in the performance, supervision, and interpretation of cardiac nuclear imaging (specifically MPI using ^{99m}Tc-labelled radiotracer) should be nuclear medicine physicians with particular expertise in nuclear cardiology (nuclear cardiologists). Cardiologists also provide much of the nuclear cardiology services. According to the Canadian Medical Association (CMA), there are 1,149 practising cardiologists in Canada.[38]

Nuclear medicine technologists are required to conduct MPI. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

All alternative imaging modalities

In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound should be diagnostic radiologists[39] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[65] According to the CMA, there are 1,149 practicing cardiologists in Canada.[38]

Medical radiation technologists (MRTs) must be certified by the CAMRT, or an equivalent licensing body. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted-part time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[65]

CTCA
CTCA is a CT-based test. In some jurisdictions, cardiologists provide much of the CTCA service. According to the CMA, there are 1,149 practicing cardiologists in Canada.[38]

For the performance of CT scan, medical radiation technologists who are certified by the CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

Stress Echo
Echo is an ultrasound-based test. Cardiologists provide much of the Echo service. A 2002 report by the CCS reported that 43% of cardiologists do Echo. According to the CMA, there are 1,149 practicing cardiologists in Canada[38] It is assumed that less than 500 of them do Echo.

Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[39] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[39] A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Stress MRI
Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Stress PET
In Canada, physicians involved in stress PET scanning should be nuclear medicine physicians, nuclear cardiologists, or cardiologists with training and expertise in nuclear imaging. In Canada, physicians who perform PET imaging studies must be certified by either the Royal College of Physicians and Surgeons of Canada or le Collège des médecins du Quebec.

Technologists must be certified by CAMRT or an equivalent licensing body. A stress technologist or dedicated physician should be on hand to monitor any procedures involving stress testing.

Table 5: Medical Imaging Professionals in Canada, 2006[39]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	MRTs	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR

Table 5: Medical Imaging Professionals in Canada, 2006[39]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**MRTs**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRT = medical radiation technologist; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; ON = Ontario; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 6 provides an overview of the availability of equipment required to conduct a preoperative assessment of patients undergoing major vascular, non-cardiac surgery. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010. Data were not available for Echo.

Table 6: Diagnostic Imaging Equipment in Canada[39,66]				
	Nuclear Medicine Cameras	**CT Scanners**	**MRI Scanners**	**PET or PET/CT**
Number of devices	603[39]	460[66]	218[66]	36[66]
Average number of hours of operation per week (2006-2007)	40	60	71	NA
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	NL, PEI, SK, YT, NT, NU

CT = computed tomography; PET = positron emission tomography; MRI = magnetic resonance imaging; NB = New Brunswick; NL. = Newfoundland; NS = Nova Scotia; NU = Nunavut; NT = Northwest Territories; PEI = Prince Edward Island; SK = Saskatchewan; YT = Yukon.

^{99m}Tc-labelled radiotracer SPECT

Nuclear medicine facilities with gamma cameras are required for SPECT imaging. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[39]

CT
No CT scanners are available in Nunavut.[39] The average weekly use of CT scanners ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[39] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[40] The average wait time for CTCA was not reported.

Echo
No information was found to identify how many Echo machines are available in Canada.

MRI
No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[39] According to Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario, with a national average of 71 hours.[39] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[40]

PET
A 2010 Environmental Scan published by CADTH reported that there are approximately 31 Canadian centres equipped to perform PET scans.[67] These centres are located in the provinces of: British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[67] There are 36 PET or PET/CT scanners in Canada, four of which are used for research purposes only.[67]

Wait times
Wait time benchmarks for cardiac nuclear imaging set by the Wait Time Alliance[68] are immediate to 24 hours for emergency cases (immediate danger to life, limb, or organ); within three days for urgent cases (situation that is unstable and has the potential to deteriorate quickly and result in an emergency admission); and within 14 days for scheduled cases (situation involving minimal pain, dysfunction, or disability — routine or elective).

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of SPECT MPI and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP; estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget — estimates here were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 7), the cost of MPI with ^{99m}Tc-based radioisotopes is $964.53. The cost of MPI with ^{201}TI or with PET is assumed to be greater than imaging with ^{99m}Tc-based radioisotopes. Stress MRI is minimally less costly than MPI with ^{99m}Tc. CTCA and stress Echo are moderately less costly.

Table 7: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[69]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
^{99m}Tc-SPECT MPI				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)	44.60	31.10	75.7
J813	Studies with ejection fraction	138.60	82.25	220.85
J807	Myocardial perfusion scintigraphy — resting, immediate post-stress	223.15	50.15	273.3
J808	MPI — delayed	82.15	27.45	109.6
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole-thallium stress test	52.05	75.00	127.05
Maintenance fees — from global budget		50.78		50.78
	TOTAL	635.93	328.6	**964.53**
^{201}Tl-SPECT MPI				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)	44.60	31.10	75.7
J813	Studies with ejection fraction	138.60	82.25	220.85
J807	Myocardial perfusion scintigraphy — resting, immediate post stress	223.15	50.15	273.3
J808	MPI — delayed	82.15	27.45	109.6
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole-thallium stress test	52.05	75.00	127.05
Maintenance fees — from global budget		50.78		50.78
	TOTAL	635.93	328.6	**964.53**
CTCA				
X235	Cardiothoracic CT		155.25	155.25
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		50.78		50.78
	TOTAL	350.78	155.25	**506.03**
Stress Echo				
G570/G571	Complete study — 1 and 2 dimensions	76.45	74.10	150.55
G577/G578	Cardiac Doppler study, with or without colour Doppler, in conjunction with complete 1 and 2 dimension Echo studies	45.15	36.90	82.05
G315/G319	Maximal stress ECG	44.60	62.65	107.25
G111/G112	Dipyridamole-thallium stress test	52.05	75.00	127.05
	TOTAL	218.25	248.65	**466.90**
Stress MRI				
X441C	MRI — thorax — multislice sequence		77.20	77.20
X445C (×3)	Repeat (another plane, different pulse sequence — to a maximum of 3 repeats)		38.65 (×3) = 115.95	115.95
X499C	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40

Table 7: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[69]				
G315/G319	Maximal stress ECG	44.60	62.65	107.25
X486C	When cardiac gating is performed (must include application of chest electrodes and ECG interpretation), add 30%		96.36	96.36
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	417.60	417.56	**835.16**
Stress PET				
J866	Myocardial perfusion scintigraphy application of SPECT (maximum 1 per examination)		31.10	31.10
J813	Studies with ejection fraction		82.25	82.25
J807	Myocardial perfusion scintigraphy — resting, immediate post-stress		50.15	50.15
J808	MPI — delayed		27.45	27.45
G315/G319	Maximal stress ECG		62.65	62.65
G111/G112	Dipyridamole-thallium stress test		75.00	75.00
Technical cost — from global budget		800.00		800.00
	TOTAL	800.00	328.60	**1128.60**

CT = computed tomography; CTCA = computed tomography coronary angiography; 3-D = three-dimensional; ECG = electrocardiogram; Echo = echocardiogram; MPI = myocardial perfusion imaging; MRI = magnetic resonance imaging; PET = positron emission tomography; Prof. = professional; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing between Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE 1946 to Present EBM Reviews - Cochrane Database of Systematic Reviews EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - Health Technology Assessment EBM Reviews - NHS Economic Evaluation Database (NHSEED) Note: Duplicates between databases were removed in Ovid.
Date of Search:	March 7, 2011
Alerts:	Monthly search updates began January 14, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	Publication years 2001 - March 2011 English language Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Multi-database Strategy	
#	Searches
	Filter: randomized controlled trials, non-randomized studies, diagnostic accuracy
1	Randomized Controlled Trial.pt.
2	Controlled Clinical Trial.pt.
3	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
4	Multicenter Study.pt.
5	(random* or sham or placebo*).ti.
6	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
7	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
8	(control* adj3 (study or studies or trial*)).ti.
9	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
10	(allocated adj "to").ti.
11	Cohort Studies/
12	Longitudinal Studies/
13	Prospective Studies/
14	Follow-Up Studies/
15	Retrospective Studies/
16	Case-Control Studies/
17	Cross-Sectional Study/
18	(observational adj3 (study or studies or design or analysis or analyses)).ti.
19	cohort.ti.
20	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
21	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
22	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
23	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
24	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
25	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
26	(population adj3 (study or studies or analysis or analyses)).ti.
27	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
28	Comparative Study.pt.
29	(Validation Studies or Evaluation Studies).pt.
30	exp "Sensitivity and Specificity"/
31	False Positive Reactions/
32	False Negative Reactions/

Multi-database Strategy	
33	"diagnostic use".fs.
34	sensitivit*.tw.
35	(predictive adj4 value*).tw.
36	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti,ab.
37	or/1-36
38	37 not case reports.pt.
	Filter: health technology assessments, systematic reviews, meta-analyses
39	meta-analysis.pt.
40	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
41	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
42	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
43	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
44	(data synthes* or data extraction* or data abstraction*).ti,ab.
45	(handsearch* or hand search*).ti,ab.
46	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
47	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
48	(meta regression* or metaregression* or mega regression*).ti,ab.
49	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
50	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
51	(cochrane or health technology assessment or evidence report).jw.
52	(meta-analysis or systematic review).md.
53	or/39-52
	Radionuclide imaging concept
54	Technetium/
55	exp Technetium Compounds/
56	exp Organotechnetium Compounds/
57	exp Radiopharmaceuticals/
58	(Technetium* or Tc-99 or Tc99 or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc*).tw,nm.
59	Radionuclide Imaging/ or Perfusion Imaging/
60	radioisotope*.mp.
61	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.

Multi-database Strategy	
62	Tomography, Emission-Computed, Single-Photon/
63	(single-photon adj2 emission*).ti,ab.
64	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
65	Radionuclide Ventriculography/
66	Myocardial Perfusion Imaging/
67	(ventriculograph* or perfusion imag*).ti,ab.
68	rMPI.ti,ab.
69	(MPI adj (test* or scan* or screen* or imag*)).ti,ab.
70	(myocardi* adj3 (imag* or tomograph* or scan*)).ti,ab.
71	(Cardiolite or Myoview).ti,ab.
72	(MIBI or sestamibi* or tetrofosmin*).ti,ab.
73	radionuclide imaging.fs.
74	or/54-73
	Preoperative assessment or operative complications concept
75	Preoperative Care/
76	Intraoperative Complications/
77	exp Postoperative Complications/
78	Perioperative care/
79	or/75-78
80	(pre-operative or preoperative or pre-surgery or pre-surgical).ti,ab.
81	(pre-operat* or preoperat* or pre-surgery or presurgery or pre-surgical or presurgical).ti,ab.
82	(operative or perioperative or peri-operative or peroperative or intraoperative or intra-operative or post-operative or postoperative).ti,ab.
83	((pre or prior or before or peri or post) adj3 (operat* or procedur* or surger*)).ti,ab.
84	(preop or pre-op or periop or peri-op).ti,ab.
85	or/80-84
86	exp Risk Assessment/
87	Risk Factors/
88	(risk* or complications or failure? or death?).ti,ab.
89	((cardiac or cardiovascular) adj3 (assess* or predict* or evaluat* or estimat* or identif* or screen* or test* or exam* or investigation*)).ti,ab.
90	or/86-89
91	(non-cardiac or noncardiac).ti,ab.
92	(major adj2 (surger* or surgical or operation?)).ti,ab.
93	exp Vascular Surgical Procedures/
94	Aortic Aneurysm, Abdominal/su [Surgery]

Multi-database Strategy	
95	(vascular surg* or abdominal surg* or intra-abdominal surg* or aortic aneurysm* or aorta aneurysm* or abdominal aneurysm* or aortic surg* or vessel surger* or vascular reconstruct* or vascular repair*).ti,ab.
96	Thoracic Surgical Procedures/
97	((thoracic or intrathoracic or intraperitoneal) adj3 (surger* or surgical or operation* or procedure*)).ti,ab.
98	or/91-97
99	79 or (85 and 90)
	Results
100	74 and 98 and 99
101	exp animals/
102	exp animal experimentation/
103	exp models animal/
104	exp animal experiment/
105	nonhuman/
106	exp vertebrate/
107	animal.po.
108	or/101-107
109	exp humans/
110	exp human experiment/
111	human.po.
112	or/109-111
113	108 not 112
114	100 not 113
115	limit 114 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CCTR,CLCMR; records were retained]
116	remove duplicates from 115
117	116 and 38
118	limit 117 to yr="2001 -Current"
119	116 and 53
120	limit 119 to yr=”2001-Current”

OTHER DATABASES	
PubMed March 8, 2011	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	Over the time range February 23 to March 11
Keywords:	Included terms for pre-operative cardiac assessment or radionuclide imaging
Limits:	Publication years 2001-present

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

APPENDIX 2.10

INDICATION OVERVIEW

Total hip arthroplasty (THA) and total knee arthroplasty (TKA) are major orthopedic procedures that can improve function and mobility and relieve pain and deformity associated with joint deterioration in appropriately selected patients.[1] Joint arthroplasty involves removing the damaged or diseased joint and replacing it with a prosthetic joint. For the hip, osteoarthritis is the most common underlying cause of joint deterioration, but inflammatory arthritic conditions, congenital or developmental defects or disorders, trauma, cancers, and osteonecrosis are also conditions that cause joint deterioration requiring THA.[1] For the knee, osteoarthritis and rheumatoid arthritis are the most common underlying causes of damage, necessitating the need for TKA; however, avascular necrosis, tumours, and congenital deformities are also underlying causes.

As with any major surgery, there is a risk of complications with joint arthroplasty.[2,3] Post-operative complications of joint arthroplasty can be categorized as early or delayed.[4] Aseptic loosening of the prosthetic joint and infection are the two most frequently encountered delayed complications, and may be suspected when a patient complains of pain in a previously healed prosthetic joint. These complications can be difficult to differentiate from one another, requiring a clinical workup, laboratory testing, and diagnostic imaging to arrive at a differential diagnosis.[4] Examples of other, less common, delayed post-operative complications associated with pain in the prosthetic joint include component failure, instability, osteolysis, heterotrophic ossification, and soft tissue syndromes.[5]

Population: Patients with joint prostheses and symptoms such as pain or fever.

Intervention: Bone scintigraphy with technetium-99m–labelled methylene diphosphonate (^{99m}Tc-MDP), technetium-99m sulphur colloid (^{99m}Tc-SC), and technetium-99m–labelled white blood cells (^{99m}Tc-WBC).

A number of nuclear imaging studies use the medical isotope ^{99m}Tc to assess painful prosthetic joints. Nuclear imaging techniques are useful in assessing orthopedic joints because the image quality is not affected by the joint prostheses, as may be the case with some other imaging techniques, such as magnetic resonance imaging (MRI) and computed tomography (CT).[6]

Bone Scintigraphy with ^{99m}Tc-MDP

Bone scintigraphy (commonly referred to as bone scanning) involves intravenous administration of the radiopharmaceutical ^{99m}Tc-MDP, which then localizes in bone.[7] ^{99m}Tc-MDP is preferentially taken up in areas with newly formed bone and images are acquired two to four hours following injection.[7] In the triple-phase bone scan, sequences of images are performed immediately following injection of the radiopharmaceutical to assess blood flow and blood pooling, 15 minutes following injection, and four hours following injection.[8] Other imaging protocols may also be used for the triple-phase bone scan, and may include delayed images taken 24 hours after injection.[7] Clearly, negative bone scintigraphy can help rule out aseptic loosening and infection;[7] however, in the case of positive bone scintigraphy, additional imaging studies may be necessary to determine the underlying cause of the positive imaging study.[7,9]

Therefore, bone scintigraphy may be considered a preliminary test that may be combined with other nuclear imaging tests to arrive at a differential diagnosis.[9,10]

^{99m}Tc-SC

A ^{99m}Tc-SC scan can be used in conjunction with white blood cells (WBCs) labelled with a radiopharmaceutical such as ^{99m}Tc hexamethylpropyleneamine oxime (^{99m}Tc-HMPAO) or Indium-111 (^{111}In) to diagnose infection as the underlying cause of pain in a prosthetic joint.[11] For the procedure, ^{99m}Tc-SC is injected intravenously and images are acquired approximately 60 to 90 minutes following injection. Following injection, ^{99m}Tc-SC accumulates in the bone marrow, allowing for its imaging. Labelled WBCs accumulate at sites of infection and in the bone. When combined, ^{99m}Tc-SC and labelled WBCs can indicate whether accumulation of the labelled WBCs is in marrow versus a site of infection. WBC accumulation without corresponding activity on marrow images suggests an infection. This is important in the assessment of prosthetic joints; hematopoietically active marrow develops around prosthetic joints, which can reduce the diagnostic accuracy of labelled WBCs if bone marrow and infection cannot be distinguished.[11]

^{99m}Tc-Labelled WBCs

Leukocytes (WBCs) labelled with ^{99m}Tc (^{99m}Tc-WBC) are used to image infections in immunocompetent patients.[9] One of the most commonly used radiopharmaceuticals to label WBCs is HMPAO, also known as exametazime.[9] ^{99m}Tc-WBCs are produced by an in vitro labelling technique in which 40 mL to 50 mL of the patient's blood is withdrawn and WBCs are separated from the erythrocytes (RBCs) and platelets.[9] The WBCs are then incubated with the radiolabel (^{99m}Tc), washed, and reinjected into the patient. The process of labelling generally takes two to three hours.[9] Images are taken within a few hours of reinjection. ^{99m}Tc-WBCs are useful for differentiating between pain due to aseptic loosening and pain associated with infection, as the labelled WBCs will migrate to areas of inflammation and infection.[9]

Comparators: For this report, the following diagnostic tests are considered as alternatives to isotope studies:

- *Positron Emission Tomography (PET; 18F-fluoride PET [^{18}F-PET] for investigation of loosening and 18F-fluorodeoxyglucose PET (^{18}FDG-PET) for investigation of infection):* PET is an imaging technique in which a radiotracer is administered. The radiotracer accumulates in a specific area of the body and emits gamma rays, which are detected by a gamma camera or PET scanner, providing details on the structure and function of organs and tissues.[12]
- *Arthrography:* Arthrography is a technique that uses fluoroscopy to image a joint following injection of contrast media directly into the joint being imaged. This technique has been used to evaluate loose prosthetic joints.[4] During the procedure, a local anesthetic is injected into the joint, followed by administration of contrast media (e.g., an iodinated contrast media or air, if the contrast media is contraindicated). A radionuclide contrast agent can also be used, such as ^{111}In or ^{99m}Tc-SC.[13] A sequence of images is then projected onto a fluorescent screen or monitor and still images are created.[14]
- *^{111}In-WBC:* ^{111}In-labelled WBCs are also used to image infections, in a manner analogous to ^{99m}Tc-labelled WBCs.[9] The technique for preparation is the same as for ^{99m} Tc-WBCs, but the compound used for labelling is ^{111}In-oxyquinoline. Disadvantages of ^{111}In-WBC include a delay of 18 to 24 hours between isotope injection and imaging and lower resolution images compared with ^{99m}Tc.[9] However, ^{111}In-WBCs have the advantage of a normal distribution of activity to the liver, spleen, and bone marrow, whereas the distribution of ^{99m}Tc-WBCs tends

to be more broad (to reticuloendothelial system, urinary tract, large intestine, and gall bladder).[9]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; Cochrane Library via Ovid; University of York Centre for Reviews and Dissemination (CRD) databases; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and prostheses.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. No date or human limits were applied for systematic reviews. For primary studies, the retrieval was limited to documents published between January 1, 2006, and February 25, 2011, and human population. The search was also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

The database search identified 754 citations, from which there were 89 articles that underwent full-text screening for inclusion in the report. Of these articles, eight systematic reviews or meta-analyses of studies of diagnostic accuracy of the tests or alternative tests were included in the report.[15-22] The remaining articles from the database search were screened to identify information pertinent to one or more of the 10 remaining criteria. Four reports were found to have relevant information.[4,10,23,24] One report was relevant to criterion 2,[4] two were relevant to criterion 4,[10,23] and one was relevant to criterion 10.[24]

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	Approximately 6,345 (2 in 10,000) Canadians undergo surgery for revision of a prosthetic joint annually.[25,26] These individuals require diagnostic imaging prior to surgery. Additional patients may undergo imaging for painful prosthetic joints, but not require surgery. Therefore, this number is likely to underestimate the total size of the affected population. The size of the affected population is likely more than 1 in 10,000 (0.01%) and less than or equal to 1 in 1,000 (0.1%)
2	**Timeliness and urgency of test results in planning patient management**	Saskatchewan guidelines for prioritization of imaging studies suggest that diagnostic imaging of a painful prosthetic joint should be performed within 8 to 30 days of test ordering.[27,28] For bone scanning specifically, guidelines suggest it be performed within 3[29] to 7[30] days of test ordering for urgent cases and 15[29] to 30[11] days for semi-urgent cases. Canadian guidelines recommend that the target time frame for imaging of painful prostheses or urgent bone scanning should be < 30 days. The target time frame for performing the ^{99m}Tc-based test is between 8 and 30 days, and obtaining the test results in the appropriate timely manner for the underlying condition has moderate impact on the management of the condition or the effective use of health care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	The most frequently cited causes of pain in prosthetic joints are not directly linked to mortality, with the exception of infection. In individuals who are immunocompetent, the risk of mortality from a bone infection is relatively low, but the presence of a prosthetic joint increases the risk of death.[31] The mortality rate in individuals with infected prosthetic joints is estimated to be 1% to 3%.[32] Based on the available information, diagnostic imaging test results have minimal impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	The clinical workup of a painful prosthetic joint includes diagnostic imaging to determine both the underlying cause and the appropriate intervention. Delay in initiating antibiotic and surgical treatment can reduce the chance of saving the prosthetic joint and preserving joint function.[31] Delay in the diagnosis of aseptic loosening can prolong patients' pain, length of disability, and impairment in function.[31] Deep infection, aseptic loosening, and prosthetic malfunction decrease quality of life, while surgical revision improves quality of life, function, and pain.[33,34]

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
		Diagnostic imaging test results can have significant impact on morbidity or quality of life.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	*Bone scanning* Limited information was identified on the acceptability of bone scanning to patients. Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. *Arthrography* Conventional arthrography is a fluoroscopic x-ray–based imaging test. Patients may have some concern over the injection of the contrast agent and the radiation exposure. In addition, patients may experience some temporary swelling in the joint. *PET* Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. *^{111}In-WBC scanning or leukocyte scanning* Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. Overall, the acceptability to the patient of bone scintigraphy with ^{99m}Tc-radiolabelled isotopes: • is moderately more acceptable than arthrography • is minimally more acceptable than ^{18}FDG-PET • is minimally more acceptable than ^{18}F-PET • has similar acceptability to patients as leukocyte scanning.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>The table presents a summary of the range of pooled estimates for the sensitivity and specificity of the tests and alternatives from the 8 included systematic reviews, by joint (hip or knee) where data were available. Single estimates are presented when only 1 meta-analysis was identified. There was no information regarding ^{18}F-PET.
<table>
<tr><th>Test</th><th>Pooled Sensitivity</th><th>Pooled Specificity</th></tr>
<tr><td>^{99m}Tc-MDP</td><td>Hip: 78%
Knee: 71%</td><td>Hip: 84%
Knee: 71%</td></tr>
<tr><td>^{99m}Tc-WBC (^{99m}Tc-HMPAO–labelled WBC)</td><td>Hip or knee: 89.0%</td><td>Hip or knee:
89.1%</td></tr>
<tr><td>^{99m}Tc-SC with ^{111}In-WBC</td><td>Hip or knee: 100.0%</td><td>Hip or knee:
91% to 98%</td></tr>
<tr><td>^{18}FDG-PET</td><td>Hip: 82% to 94%
Knee: 87% to 98%</td><td>Hip: 90% to 93%
Knee:75% to 79%</td></tr>
<tr><td>Arthrography</td><td>Subt — hip:
86% to 89%
Nuclear — Hip: 85% to 87%</td><td>Subt — hip:
76% to 85%
Nuclear — hip: 64% to 83%</td></tr>
<tr><td>^{111}In-WBC</td><td>Hip or knee: 82.8%</td><td>Hip or knee: 83.8%</td></tr>
</table>
^{18}FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; ^{111}In-WBC = Indium-111 white blood cell; subt = subtraction; ^{99m}Tc-MDP = technetium-99m–labelled methylene diphosphonate; ^{99m}Tc-SC = technetium-99m sulphur colloid; ^{99m}Tc-WBC = technetium-99m–labelled white blood cells.

For patients with suspected prosthesis loosening, the diagnostic accuracy of bone scanning with ^{99m}Tc-radiolabelled isotopes is:</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		• similar to arthrography • similar to ^{18}F-PET. For patients with suspected infection, the diagnostic accuracy of bone scanning with ^{99m}Tc-radiolabelled isotopes is: • similar to arthrography • moderately better than ^{18}FDG-PET • moderately lower than leukocyte scanning.
8	**Relative risks associated with the test**	**Non–radiation-related risks** *Bone scanning* Mild adverse events (AEs) with ^{99m}Tc-labelled tracers (i.e., skin reactions) have been reported.[35-38] Serious AEs have been reported with ^{99m}Tc-labelled SC (e.g., cardiopulmonary arrest, seizures, and anaphylactic shock), although rates were not provided.[37] *Arthrography* Patients may experience some temporary swelling in the joint and experience reactions to the contrast agent, if used. *^{18}FDG-PET* The Pharmacopeia Committee of the Society of Nuclear Medicine conducted a 4-year prospective evaluation of AEs with PET and reported no AEs in 33,925 scans in 22 PET centres in the United States.[39] *Leukocyte (WBC) scan* Mild AEs with ^{99m}Tc-labelled tracers, including those used to label WBC (e.g., skin reactions), have been reported, although no reaction rates were provided.[35,38,40] **Radiation-related Risks** Among the modalities to diagnose cause of painful prostheses, ^{99m}Tc-MDP, ^{99m}Tc-SC, ^{99m}Tc-WBC, and PET expose the patient to ionizing radiation. Overall, bone scintigraphy with ^{99m}Tc-radiolabelled isotopes is: • moderately safer than arthrography • minimally safer than ^{18}FDG-PET • minimally safer than ^{18}F-PET

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		• minimally safer than leukocyte scanning.
9	**Relative availability of personnel with expertise and experience required for the test**	As of 2006 in Canada, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, and 1,781 nuclear medicine technologists available across Canada. Yukon, Northwest Territories, and Nunavut do not have the available personnel to perform and interpret tests to investigate the cause of painful prostheses. Other jurisdictions (e.g., Prince Edward Island) may offer limited nuclear medicine services. Assuming the equipment is available, if bone scanning using ^{99m}Tc is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using arthrography • fewer than 25% of the procedures can be performed in a timely manner using ^{18}FDG-PET • fewer than 25% of the procedures can be performed in a timely manner using ^{18}F-PET • 75% to 94% of the procedures can be performed in a timely manner using leukocyte scanning.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>10</td><td>Accessibility of alternative tests (equipment and wait times)</td><td>No nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[41] The average wait time for urgent bone scan in 2010 ranged from 1 to 6 days, and for non-urgent scans, ranged from 7 to 73 days.[42]

As of November 2010, there were approximately 31 Canadian centres performing publicly funded PET scans.[43] These centres are all located in British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[43]

Assuming the necessary expertise is available if bone scanning using ^{99m}Tc is not available, it is estimated that:

• more than 95% of the procedures can be performed in a timely manner using arthrography
• fewer than 25% of the procedures can be performed in a timely manner using ^{18}FDG-PET
• fewer than 25% of the procedures can be performed in a timely manner using ^{18}F-PET
• 75% to 94% of the procedures can be performed in a timely manner using leukocyte scanning.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of bone scan with ^{99m}Tc-based radioisotopes is $323.11. Arthrography is the only less costly alternative. Leukocyte scan is moderately more costly. ^{18}F-PET and ^{18}FDG-PET are significantly more costly.

Relative Costs
<table>
<tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr>
<tr><td>Bone scan</td><td>323.11</td><td>Reference</td></tr>
<tr><td>Arthrography</td><td>171.07</td><td>-152.04</td></tr>
<tr><td>Leukocyte scan</td><td>586.01</td><td>+262.90</td></tr>
<tr><td>^{18}F-PET</td><td>850.00</td><td>+526.89</td></tr>
<tr><td>^{18}FDG-PET</td><td>1050.00</td><td>+726.89</td></tr>
</table></td></tr>
</table>

AE = adverse event; CT = computed tomography; FDG = fluorodeoxyglucose; ^{18}FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; ^{111}In-WBC = Indium-111 white blood cell; MDP = methylene diphosphonate; mSv = millisievert; PET = positron emission tomography; SC = sulphur colloid; subt = subtraction; ^{99m}Tc- HMPAO = technetium-99m hexamethylpropyleneamine oxime; ^{99m}Tc-MDP = technetium-99m methylene diphosphonate; ^{99m}Tc-SC = technetium-99m sulphur colloid; ^{99m}Tc-WBC = technetium-99m–labelled white blood cells; WBC = white blood cell.

CRITERION 1: Size of affected population (link to definition)

In Canada, information on the level of activity, clinical parameters, and outcomes of primary and revision hip and knee replacement operations over time is captured by the Canadian Joint Replacement Registry. All hospitals in Canada report information to the registry on joint replacements and revisions to joint replacements.[26] Based on data from 2006 to 2007, there were 24,253 hospitalizations for THA and 37,943 hospitalizations for TKA (62,196 joint replacements in total) in Canada, excluding the province of Quebec. From 1996-1997 to 2006-2007, there was a 59% increase in the number of THAs and a 140% increase in the number of TKAs. The majority of patients who undergo total joint arthroplasty are older than 65 years (63% of hip and 64% of knee replacement recipients),[26] which would suggest population aging will continue to increase the demand for these procedures.[31]

Across Canada, approximately 13.6% of the hospitalizations for THA were for revisions to a joint that had previously been replaced. The most common reasons for revision were aseptic loosening (44%), osteolysis (22%), poly wear (21%), and instability (13%). For TKA, the percentage of revisions was 6.3%, with the most common reasons for revision being aseptic loosening (25%), poly wear (17%), infection (16%), and instability (14%).

Quebec data from 2004-2005 indicate that there were 4,129 hip replacements (462 revisions) and 5,123 knee replacements (340 revisions).[25]

If it is assumed that all patients who undergo revision require imaging studies prior to surgery, approximately 5,543 patients would require imaging, based on 2006-2007 data. Based on 2004-2005 data, an additional 802 patients from Quebec would require imaging prior to surgical revision, making the total across Canada approximately 6,345, translating to an incidence of approximately two per 10,000 persons in Canada. This would exclude patients who would undergo imaging for a painful prosthetic joint but not require surgery, and likely represents an underestimation of the use of ^{99m}Tc-based imaging.

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

In the evaluation of a painful prosthetic joint, a clinical workup, laboratory testing, and diagnostic imaging is needed to arrive at a differential diagnosis in order for a patient to receive appropriate treatment.[4] A distinction between aseptic loosening, septic loosening, and infection is necessary for patients to undergo surgical revision if needed. A delay in imaging could potentially delay treatment of an infection, placing the patient at risk for loss of the prosthetic joint due to delay of surgery, and prolongation of the patient's pain, length of disability, and impairment in function.[32]

According to Saskatchewan guidelines for prioritization of imaging studies, diagnostic imaging of a painful prosthetic joint would likely be considered a Level 3 priority, suggesting the need for imaging within eight to 30 days from test ordering (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). According to Canada's Wait Time Alliance, bone scanning should be performed within seven days of test ordering for urgent cases and 30 days for semi-urgent cases,[30] while the Canadian Society for Nuclear Medicine recommends that urgent and non-urgent bone scans be performed within three and 15 days, respectively.[29]

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

The most frequently cited causes of pain in prosthetic joints are not directly linked to mortality, with the exception of infection. In individuals who are immunocompetent, the risk of mortality from a bone infection is relatively low, but the presence of a prosthetic joint increases the risk of death.[31] The mortality rate in individuals with infected prosthetic joints is estimated to be 1% to 3%.[32]

Diagnosis of prosthetic joint infections has been described as difficult and complex.[32] The diagnosis of infection in a prosthetic joint often requires one or more nuclear imaging study that may involve ^{99m}Tc; for example, labelled WBC imaging combined with bone marrow imaging using ^{99m}Tc-SC.[32] The majority of patients with prosthetic joint infections require surgical debridement or removal of the prosthetic joint, in addition to treatment with antibiotics.[32] A delay in imaging could delay a differential diagnosis of infection and appropriate treatment, thereby increasing the risk of death.

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

The evaluation of a painful prosthetic joint includes diagnostic imaging to determine the underlying cause.[2,3] Delays in diagnostic imaging can delay the differential diagnosis between aseptic loosening and joint infection, which are two complications that are considered more difficult to diagnose. Other complications, such as heterotrophic ossification, fracture, and dislocation, are less frequently encountered and easier to diagnose.[10] While prosthetic joint infection occurs less frequently than aseptic loosening, it has been associated with high morbidity and cost.[23] Delaying the initiation of antibiotic and surgical treatment (revision, debridement, or removal) can reduce the chance of saving the prosthetic joint and preserving joint function.[31] Delay in the diagnosis of aseptic loosening can prolong patient's pain, length of disability, and impairment in function.[31]

Deep infection, aseptic loosening, and prosthetic malfunction following joint arthroplasty have been associated with decreased health-related quality of life compared with baseline preoperative values.[34] Thus, a delay in differential diagnosis and, therefore, treatment would likely prolong the detrimental effects on health-related quality of life.

Surgical revision in patients with aseptic or septic loosening improves pain, function, and stiffness on the Western Ontario and McMaster Universities Arthritis Index (WOMAC — an osteoarthritis-specific health-related quality of life measure) and improves Harris Hip Scores (a measure of hip function following surgery).[44] Similarly, patients who undergo revision TKAs for aseptic loosening or infection experience gains in physical and mental health measured using the 36-item Short Form Health Survey (SF-36, a generic health status measure that captures eight domains of health: vitality, physical functioning, pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, mental health), gains in function (ability to walk and climb stairs), and improvements in Knee Society Scores, which capture pain, stability, and range of motion.[33]

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CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

Residents of rural and remote areas
In Canada, there is geographic variation in access to nuclear medicine imaging studies and alternative tests, due to a lack of availability, equipment, and expertise in some areas, in particular the Yukon, Northwest Territories, and Nunavut.[45] As many of the tests and alternatives used for assessment of painful prosthetic joints involve radiopharmaceuticals, geographic access could potentially be similar for imaging techniques involving ^{99m}Tc, and ^{111}In. This suggests that the alternate tests may not reduce the health disparities of those who live in rural and remote areas, where availability of imaging with ^{99m}Tc may be limited.

For the alternative test ^{18}FDG-PET, availability may be particularly limited in that due to the short half-life of the isotope, the imaging study must be performed at a centre close to a cyclotron that produces FDG.[46] This could limit access for individuals in remote areas or for those who do not live close by or could not travel to the facility where ^{18}FDG-PET is available.

Age
The majority of joint replacements are performed in individuals older than 65 years.[26] Thus, individuals who require diagnostic imaging to assess painful prosthetic joints would generally be in this age group. As such, imaging studies, along with laboratory and clinical workups, could potentially improve quality of life in patients with painful prosthetic joints to help expedite the diagnosis of an underlying cause and treatment (antibiotics, surgical revision, or removal). However, no evidence was identified from the searches to suggest one test or alternative might have greater potential to reduce the health disparity of older adults with painful prosthetic joints.

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

Bone scanning
Limited information was identified on the acceptability of bone scanning to patients. Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

Arthrography
Conventional arthrography is a fluoroscopic x-ray–based imaging test. Local anesthetic and contrast agent are injected into the joint space. Patients may have some concern over the injection of the contrast agent and the radiation exposure. In addition, patients may experience some temporary swelling in the joint.

PET
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

^{111}In-WBC
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Eight systematic reviews with or without meta-analysis were identified that summarized the diagnostic accuracy of the tests and alternatives used for the evaluation of painful prosthetic joints.[15-22] Details of these studies are summarized in Appendix 3, Table 7. No studies were identified that compared ^{99m}Tc-based imaging with ^{18}F-PET.

Van der Bruggen et al.[15] performed a systematic review of the literature (without meta-analysis) to determine the diagnostic accuracy of the combination of ^{111}In-WBC and ^{99m}Tc-SC, the combination of ^{111}In-WBC and ^{99m}Tc-MDP, ^{111}In-WBC alone, and ^{18}FDG-PET in the diagnosis of prosthetic bone and joint infections. Other indications, unrelated to this literature summary, were also included in the review but are not presented. There were nine relevant studies of the tests and alternatives included in Van der Bruggen et al.'s systematic review. The quality of these studies was not reported.

The sensitivity and specificity of the combination of ^{111}In-WBC and ^{99m}Tc-SC were 100% and 91% to 98%, respectively. The sensitivity and specificity of the combination of ^{111}In-WBC and ^{99m}Tc-MDP were 95% to 97% and 91% to 98%, respectively. For ^{111}In-WBC alone, the sensitivity and specificity were 87% to 100% and 53% to 94%, respectively. The included studies of ^{18}FDG-PET had a wide range of sensitivity (28% to 91%) and specificity (9% to 97%) for the diagnosis of infection of a prosthetic joint. The authors concluded that when relying on conventional scintigraphy, osteomyelitis was best detected using the combination of ^{111}In-WBC and ^{99m}Tc-MDP. Despite the wide ranges reported for both sensitivity and specificity, the authors further concluded that using ^{18}FDG-PET to detect osteomyelitis was feasible and had adequate sensitivity and specificity.

Reinartz[16] performed a systematic review of the literature and meta-analysis to determine the diagnostic accuracy of a triple-phase bone scan (TPBS) with ^{99m}Tc-MDP, WBC imaging, and ^{18}FDG-PET in patients with painful prosthetic hip or knee joints. In this systematic review, diagnostic accuracy was not determined separately for loosening or suspected infection, but data for hip and knee joints were presented separately.

For the assessment of diagnostic accuracy of labelled WBCs, ^{111}In and ^{99m}Tc were analyzed together, and it is important to note that half of the studies actually combined labelled WBCs with a bone scan (n = 2) or bone marrow scan (n = 5). This must be considered when interpreting the sensitivity and specificity of labelled WBCs. The gold standard was unclear for all studies, study quality was not reported, and the methods of the systematic review and meta-analysis were poorly described.

A total of 43 studies were included. For the hip, the sensitivities of TPBS, labelled WBCs, and ^{18}FDG-PET were 78%, 76%, and 85%, respectively, while the specificities were 84%, 96%, and 90%, respectively. For the knee, the sensitivities of TPBS, labelled WBCs, and ^{18}FDG-PET were 87%, 95%, and 98%, respectively, while the specificities were 71%, 81%, and 75%, respectively. The authors concluded that ^{18}FDG-PET is an effective imaging technique for diagnosing complications related to TKA and THA and they would recommend it. They further concluded that WBC imaging combined with bone marrow imaging should still be considered the gold standard, but is complex and time consuming.

Zoccali et al.[17] performed a systematic review and meta-analysis of the ability of ^{18}FDG-PET to differentiate between septic and aseptic loosening of prosthetic hip joints. Five studies were included in the meta-analysis, the quality of which was not reported; nor was the gold standard used in assessing diagnostic accuracy. The pooled sensitivity for infection of the prosthetic joint was 82.8%. Specificity data were not pooled, and ranged from 77.8% to 96.6% across studies. The authors concluded that the sensitivity and specificity of ^{18}FDG-PET confirm its importance in the future for evaluating painful prosthetic hip joints.

Kwee et al.[18] performed a systematic review with meta-analysis of the diagnostic accuracy of ^{18}FDG-PET for the diagnosis of infection in a prosthetic hip or knee joint. Eleven relevant studies were included, with median quality ratings of 82% (82% of items on a checklist of internal or external validity criteria were met). The gold standard for diagnostic accuracy differed across studies, but generally included multiple criteria. Most studies included a systemic infection, microorganism culture from joint aspiration, or positive culture from surgery as a criterion. This was in addition to clinical and laboratory findings. The pooled sensitivity and specificity for infection of a prosthetic hip were 82.1% and 89.9%, respectively. The pooled sensitivity and specificity for infection of a prosthetic knee were 86.6% and 74.8%, respectively. The authors concluded that the diagnostic accuracy of ^{18}FDG-PET was moderate to high, but that caution was warranted as the studies were heterogeneous.

Zhuang et al.[19] performed a systematic review with meta-analysis of the diagnostic accuracy of ^{18}FDG-PET for the evaluation of prosthetic joint pain. The methodology of the review was poorly reported. A total of eight relevant studies were identified, the quality of which was not reported; nor was the gold standard for diagnostic accuracy. The pooled sensitivity and specificity for infection of a prosthetic hip was 85.5% and 92.6%, respectively. The pooled sensitivity and specificity for infection of a prosthetic knee were 94.4% and 79.2%, respectively. The authors concluded that ^{18}FDG-PET should play an important role in distinguishing between aseptic loosening from bone infection.

Temmerman et al. (2007)[20] conducted a systematic review with meta-analysis of the diagnostic accuracy of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy for loosening of the acetabular component of total hip prostheses. Bone scintigraphy was performed with a number of isotopes, including ^{99m}Tc and ^{67}Ga, among others. The isotopes used for nuclear arthrography were not reported. In total, 28 studies were included, all of which had a quality rating of 4 on a five-point scale (with 1 being the highest quality).

Plain radiography (which was not one of the tests or alternatives considered for this evidence summary, but is included here for comparative purposes) had a sensitivity of 70% and a specificity of 80%. Subtraction arthrography, nuclear arthrography, and bone scintigraphy had sensitivities of 89%, 87%, and 67%, respectively, and specificities of 76%, 64%, and 75%, respectively. The authors concluded that subtraction arthrography should be used to complement plain radiography when the results of plain radiography are inconclusive.

Prandini et al.[21] evaluated the diagnostic accuracy of ^{99m}Tc-HMPAO WBCs, ^{99m}Tc- TPBS, ^{67}Ga scan, ^{111}In WBCs, and ^{18}FDG-PET for the detection of bone infection due to a prosthetic joint or a peripheral open fracture. Data for the two indications were pooled together in the analysis. Ninety studies were included in the review. No information on methodological quality of the included studies was reported. For ^{99m}Tc-HMPAO WBCs, the sensitivities were 89% and 85.4%, respectively, while the specificities were 89.1% and 75.2%, respectively. For the alternate tests,

the sensitivities were 70.1% with ^{67}Ga scan, 82.8% with ^{111}In WBCs, and 94.1% with ^{18}FDG-PET, while the specificities for these tests were 81.8%, 83.8%, and 87.3%, respectively. The authors concluded that ^{18}FDG-PET was the most accurate method for diagnosing bone infections, but had lower specificity than ^{99m}Tc-HMPAO WBCs.

Temmerman et al. (2005)[22] conducted a systematic review with meta-analysis of the diagnostic accuracy of plain radiography, subtraction arthrography, nuclear arthrography, and bone scintigraphy for loosening of the femoral component of total hip prostheses. Again, studies of scintigraphy with different isotopes, such as ^{99m}Tc and ^{67}Ga, were pooled together for the analysis and the isotopes used for nuclear arthrography were not reported.

In total, 51 studies were included, all of which had a quality rating of 4 on a five-point scale (with 1 being the highest quality). Plain radiography had a sensitivity of 82% and a specificity of 81%. Subtraction arthrography, nuclear arthrography, and bone scintigraphy had sensitivities of 86%, 85%, and 85%, respectively, and specificities of 85%, 83%, and 72%, respectively. The authors concluded that plain radiography and scintigraphy are the preferred techniques for evaluating the femoral component of prosthetic hip, due to the lower morbidity risk to the patient.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Bone scanning
Several studies[35-38] reported mild AEs with ^{99m}Tc-labelled tracers(e.g., skin reactions) and one identified article[37] reported serious AEs with ^{99m}Tc-labelled sulphur colloid (e.g., cardiopulmonary arrest, seizures, and anaphylactic shock). No reaction rates were provided.

Arthrography
Patients may experience some temporary swelling in the joint.

^{18}F-PET and ^{18}FDG-PET
The Pharmacopeia Committee of the Society of Nuclear Medicine conducted a four-year prospective evaluation of adverse reactions to PET and reported no adverse reactions among the 33,925 scans conducted in 22 participating PET centres in the United States.[39]

Leukocyte (WBC) scan
Several studies[35,38,40] reported mild AEs with ^{99m}Tc-labelled tracers, including those used to label WBC (e.g., skin reactions). No reaction rates were provided.

Radiation-related Risks

Among the modalities to diagnose cause of painful prostheses, ^{99m}Tc-MDP, ^{99m}Tc-SC, ^{99m}Tc-WBC and CT, PET, and arthrography expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 2. Although different radiopharmaceuticals can be used for the diagnosis of painful prostheses, ^{99m}Tc-MDP, ^{99m}Tc-SC, and ^{99m}Tc-WBC are the most commonly used to evaluate painful prostheses. As the table shows, ^{67}Ga delivers larger doses of radiation than ^{99m}Tc-labelled radiopharmaceuticals.

Table 2: Effective Radiation Exposure from Imaging Studies	
Imaging Study	**Estimated Radiation Dose (mSv)**
^{99m}Tc-HMPAO	6.9[47]
^{99m}Tc-MDP	4.2[47]
^{99m}Tc-SC	2.8[47]
^{99m}Tc-WBCs	8.1[47]
^{111}In-WBCs	6.7[47]
^{99m}Tc-MDP bone scan	4.2[47]
^{18}FDG-PET	7.0[47]
X-ray of knee	0.8 mSv[48]
X-ray of knee	< 0.1 mSv[48]
Average background dose of radiation per year	1 to 3.0[49-51]

^{18}FDG-PET = 18F-fluorodeoxyglucose positron emission tomography; ^{111}In-WBC = Indium-111 white blood cell; mSv = millisievert; ^{99m}Tc- HMPAO = technetium-99m hexamethylpropyleneamine oxime; ^{99m}Tc-MDP = technetium-99m methylene diphosphonate; ^{99m}Tc-SC = technetium-99m sulphur colloid; ^{99m}Tc-WBC = technetium-99m–labelled white blood cells.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

Bone scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of bone scans should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[52] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct bone scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans should be diagnostic radiologists[45] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[52]

Medical radiation technologists (MRTs) must be certified by CAMRT or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[52]

Arthrography

Arthrography involves the use of fluoroscopy to image a joint. Diagnostic Radiologists should be responsible for the performance, supervision, and interpretation of fluoroscopy.[53] Evidence of training in fluoroscopic procedures is required for physicians who use fluoroscopy without supervision of a radiologist and/or x-ray technologist. An MRT is responsible for performing the exam and image technical evaluation and quality. The MRT should have specialized training in fluoroscopy and perform fluoroscopy on a regular basis.

PET

In Canada, physicians involved in the performance, supervision, and interpretation of PET scans should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Technologists must be certified by CAMRT or an equivalent licensing body.

Leukocyte scan

Leukocyte scanning requires the same personnel as bone scanning with ^{99m}Tc-based radioisotopes. No literature was identified regarding the expertise required for handling and processing of white blood cells.

Table 3 Medical Imaging Professionals in Canada

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	Medical Radiation Technologists	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322**

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdictions; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PEI = Prince Edward Island; QC = Quebec; YT = Yukon.

*This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 4 provides an overview of the availability of equipment required to evaluate patients with

painful prostheses. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Information on the availability of PET and PET/CT scanners is current to November 30, 2010.

Table 4: Diagnostic Imaging Equipment in Canada[41,43,45]

	Nuclear Medicine Cameras	SPECT/CT Scanners	PET or PET/CT Scanners
Number of devices	603[45]	96[41]	36[43]
Average number of hours of operation per week (2006-2007)[45]	40	NA	NA
Provinces and Territories with no devices available	YT, NT, NU	PEI, YT, NT, NU	NL, PEI, SK, YT, NT, NU

MRI = magnetic resonance imaging; NA = not available; NL = Newfoundland and Labrador; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; PET = positron emission tomography; SK = Saskatchewan; SPECT/CT = single-photon emission computed tomography/computed tomography; YT = Yukon.

Bone scanning
For bone scintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[45]

PET
A 2010 Environmental Scan published by CADTH reported that approximately 31 Canadian centres are equipped to perform PET scans.[43] These centres are located in the provinces of British Columbia, Alberta, Manitoba, Ontario, Quebec, New Brunswick, and Nova Scotia.[43] There are 36 PET or PET/CT scanners, four of which are used for research purposes only.[43]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of bone scanning and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical or surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 5), the cost of bone scan with ^{99m}Tc-based radioisotopes is $323.11. Arthrography is the only less costly alternative. Leukocyte scan is moderately more costly. ^{18}F-PET and ^{18}FDG-PET are significantly more costly.

Table 5: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[54]

Fee code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
Bone scan				

J867	Blood flow and pool imaging	58.75	29.30	88.05
J851	Bone scintigraphy — single site	87.00	50.95	137.95
J866	Application of tomography (SPECT)	44.60	31.10	75.70
Maintenance fees — global budget		21.41		21.41
	TOTAL	211.76	111.35	**323.11**
Arthrography				
X196	Fluoroscopy — skeleton	9.50	14.95	24.45
J001	Arthrogram, tenogram, or bursogram		29.55 (Spec) 105.07 (Anes)	134.62
	Maintenance fees — global budget	12.00		12.00
	TOTAL	21.50	149.57	**171.07**
Leukocyte scan				
J884B/J884C	^{111}In leukocyte scintigraphy — single site	329.00	50.95	379.95
J866B/J866C	Application of tomography (SPECT)	44.60	31.10	75.7
J867B/J867C	First transit — with blood pool images	58.75	29.30	88.05
Maintenance fees — from global budget		42.31		42.31
	TOTAL	474.66	111.35	**586.01**
^{18}F-PET				
Professional fee for PET			250.00	250.00
Technical cost — from global budget		600.00		600.00
	TOTAL	800.00	250.00	**850.00**
^{18}FDG-PET				
Professional fee for PET			250.00	250.00
Technical cost — from global budget		800.00		800.00
	TOTAL	800.00	250.00	**1,050.00**

Anes = anesthetic; ^{18}F-PET = 18F- fluoride positron emission tomography; ^{18}FDG-PET = 18F-fluorodeoxyglucose position emission tomography; ^{111}In = Indium-111; PET = positron emission tomography; prof. = professional; spec = specialist; SPECT = single-photon emission computed tomography; tech. = technical.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the technetium-99m (^{99m}Tc)-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to February 25, 2011 EBM Reviews - ACP Journal Club 1991 to February 2011 EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011 EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 2011 EBM Reviews - Cochrane Methodology Register 1st Quarter 2011 EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2011 EBM Reviews - Health Technology Assessment 1st Quarter 2011 **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	February 25, 2011
Alerts:	Monthly search updates began February 25, 2011 and ran until October, 2011
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, none-randomized studies, and diagnostic accuracy studies.
Limits:	Publication years 2006-February 25, 2011 for primary studies; no date limits for systematic reviews English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading Word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.tw	Text word
.nm	Name of substance word
.mp	Mapped word
.jw	Journal words
/ri	Radionuclide imaging

Multi-Database Strategy	
#	**Searches**
1	exp "Prostheses and Implants"/ or exp joint prosthesis/ or exp arthroplasty, replacement/ or prosthesis-related infections/ or prosthesis failure/
2	(prostheses or prosthesis or prosthetic* or periprosthetic* or arthroplast*).ti,ab.
3	((bone* or joint* or knee* or hip or hips or ankle* or finger* or shoulder* or elbow* or joint or joints or lumbar) adj3 (replace* or replacing* or replacement* or artificial or implant*)).ti,ab.
4	or/1-3
5	Technetium/ or exp Technetium Compounds/ or exp Organotechnetium Compounds/ or exp Radiopharmaceuticals/
6	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.
7	Radionuclide Imaging/ or Perfusion Imaging/
8	radionuclide imaging.fs.
9	radioisotope*.mp.
10	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
11	Tomography, Emission-Computed, Single-Photon/
12	(single-photon adj2 emission*).ti,ab.
13	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
14	(HMPAO or Tc-MDP or HM-PAO).tw, nm.
15	exp Joints/ri
16	exp "bone and bones"/ri
17	Bone marrow/ri
18	Osteomyelitis/ri
19	((bone or bones or joint or joints) adj2 (scan* or imag* or scintigraph*)).ti,ab.
20	or/5-19
21	4 and 20
22	((prosthes* or arthroplast*) adj2 (scan* or imag* or scintigraph*)).ti,ab.
23	21 or 22
24	meta-analysis.pt.
25	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
26	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
27	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
28	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
29	(data synthes* or data extraction* or data abstraction*).ti,ab.
30	(handsearch* or hand search*).ti,ab.
31	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
32	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
33	(meta regression* or metaregression* or mega regression*).ti,ab.
34	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
35	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
36	(cochrane or health technology assessment or evidence report).jw.

Multi-Database Strategy	
37	(meta-analysis or systematic review).md.
38	or/24-37
39	23 and 38
40	exp "Sensitivity and Specificity"/
41	False Positive Reactions/
42	False Negative Reactions/
43	du.fs.
44	sensitivit*.tw.
45	(predictive adj4 value*).tw.
46	Comparative Study.pt.
47	(Validation Studies or Evaluation Studies).pt.
48	Randomized Controlled Trial.pt.
49	Controlled Clinical Trial.pt.
50	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
51	Multicenter Study.pt.
52	(random* or sham or placebo*).ti.
53	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
54	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
55	(control* adj3 (study or studies or trial*)).ti.
56	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
57	(allocated adj "to").ti.
58	Cohort Studies/
59	Longitudinal Studies/
60	Prospective Studies/
61	Follow-Up Studies/
62	Retrospective Studies/
63	Case-Control Studies/
64	Cross-Sectional Study/
65	(observational adj3 (study or studies or design or analysis or analyses)).ti.
66	cohort.ti.
67	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
68	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
69	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
70	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
71	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
72	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
73	(population adj3 (study or studies or analysis or analyses)).ti.
74	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
75	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).tw.
76	or/40-75
77	76 not case reports.pt.
78	23 and 77
79	remove duplicates from 78

Multi-Database Strategy	
80	limit 79 to english language [Limit not valid in ACP Journal Club,CCTR,CDSR,CLCMR,DARE; records were retained]
81	80 use pmez
82	limit 81 to yr="2006-current" [Limit not valid in DARE; records were retained]
83	80 use acp,cctr,coch,dare,clcmr,clhta
84	82 or 83
85	exp animals/
86	exp animal experimentation/
87	exp models animal/
88	exp animal experiment/
89	nonhuman/
90	exp vertebrate/
91	animal.po.
92	or/85-91
93	exp humans/
94	exp human experiment/
95	human.po.
96	or/93-95
97	92 not 96
98	84 not 97
99	remove duplicates from 39
100	from 98 keep 1-397
101	limit 99 to english language [Limit not valid in ACP Journal Club,CCTR,CDSR,CLCMR,DARE; records were retained]

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Grey Literature Search	
Dates for Search:	February to March 2011
Keywords:	Included terms for prostheses and radionuclide imaging
Limits:	Publication years 2006 to Feb/March 2011 for primary studies; no date limits for systematic reviews and guidelines

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters), were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Diagnostic Accuracy

Table 7: Diagnostic Accuracy of Tests and Alternatives Based on the Information Presented in the Included Studies

Study	Tests and Indication	Study Eligibility	Number of Included Studies	Search	Quality of Included Studies	Diagnostic Accuracy versus Gold Standard		
van der Bruggen et al. 2010[15]	^{111}In-WBC with ^{99m}Tc-SC ^{111}In-WBC with ^{99m}Tc-MDP ^{111}In-WBC FDG-PET Diagnosis of prosthetic bone and joint infections	English language Case reports, meeting reports, editorials, letters excluded. Animal studies and studies with < 5 patients excluded.	^{111}In-WBC with ^{99m}Tc-SC — 2 ^{111}In-WBC with ^{99m}Tc-MDP — 2 FDG-PET — 3 ^{111}In-WBC — 2	1980 to 2008	Not reported	**^{111}In-WBC with ^{99m}Tc-SC (GS not reported)**	**^{111}In-WBC with ^{99m}Tc-MDP (GS not reported)**	**Alternative tests**
						Sensitivity†: 100% Specificity†: 91% to 98%	Sensitivity†: 95% to 97% Specificity†: 93% to 100%	**^{111}In-WBC (GS not reported)** Sensitivity†: 87% to 100% Specificity†: 53% to 94% **FDG-PET (Variable GS)** Sensitivity†: 28% to 91% Specificity†: 9% to 97%
Reinartz 2009[16]	Triple-phase bone scan (^{99m}Tc-MDP) WBC imaging FDG-PET Diagnosis of pathological processes of hip and knee	Diagnostic procedure performed according to guidelines Could determine sensitivity and specificity from the data Patient cohort	TPBS — 16 WBCs — 14 FDG-PET — 13	1988 to 2008	Not reported	**TPBS (GS not Reported)**	**Labelled WBCs (GS not Reported)**	**FDG-PET (GS not Reported)**
						Hip: Sensitivity: 78% Specificity: 84% Knee: Sensitivity: 87% Specificity: 71%	Hip: Sensitivity: 76% Specificity: 96% Knee:	Hip: Sensitivity: 85% Specificity: 90% Knee: Sensitivity: 98% Specificity: 75%

Table 7: Diagnostic Accuracy of Tests and Alternatives Based on the Information Presented in the Included Studies								
Study	**Tests and Indication**	**Study Eligibility**	**Number of Included Studies**	**Search**	**Quality of Included Studies**	**Diagnostic Accuracy versus Gold Standard**		
	arthroplasty.	not too specialized (e.g., a single new type of prosthesis) Minimum 6-month follow-up.				Mixed study population (hip or knee):† Sensitivity: 33% to 100% Specificity: 0% to 86%	Sensitivity: 95% Specificity: 81% Mixed study population (hip or knee):† Sensitivity: 80% to 100% Specificity: 71% to 91%	Mixed study population (hip or knee):‡ Sensitivity: 36% Specificity: 97%
Zoccali et al. 2009[17]	FDG-PET Differential diagnosis of septic and aseptic loosening of prosthetic hip joints	Prospective studies to detect loosening PET performed ~ 1 year following surgery Images evaluated by 1 to 2 experts Minimum 6-month follow-up	5	Up to 2007	Not reported	**FDG-PET — Hip for Infection (GS not reported)**		
						Sensitivity: 82.8% Specificity†: –77.8% to 96.6%		

Table 7: Diagnostic Accuracy of Tests and Alternatives Based on the Information Presented in the Included Studies								
Study	**Tests and Indication**	**Study Eligibility**	**Number of Included Studies**	**Search**	**Quality of Included Studies**	**Diagnostic Accuracy versus Gold Standard**		
Kwee et al. 2008[18]	FDG-PET Diagnosis of prosthetic joint infection.	Diagnostic performance of FDG-PET for prosthetic hip or knee infection. No restriction on reference standard, other than could not include FDG-PET. Excluded review articles, meta-analyses, abstracts, editorials, case reports, guidelines, animal and ex vivo studies, studies with fewer than 15 patients, studies that used FDG with a gamma camera and studies with insufficient data to determine sensitivity and specificity.	11	Up to 2008 (no beginning date limit)	Assessed with a checklist for internal and external validity Scores presented as a percentage of maximum and ranged from 45% to 91% (median of 82%).	**FDG-PET — Hip (Variable GS)**	**FDG-PET — Knee (Variable GS)**	**FDG-PET — Knee and hip pooled (Variable GS)**
						Sensitivity: 82.1% Specificity: 89.8%	Sensitivity: 86.6% Specificity: 74.8%	Sensitivity: 84.6% Specificity: 84.0%

Table 7: Diagnostic Accuracy of Tests and Alternatives Based on the Information Presented in the Included Studies								
Study	**Tests and Indication**	**Study Eligibility**	**Number of Included Studies**	**Search**	**Quality of Included Studies**	**Diagnostic Accuracy versus Gold Standard**		
Zhuang et al. 2007[19]	FDG-PET Evaluation of painful prosthetic joints	English language studies No other criteria reported	8	Not reported	Not reported	**FDG-PET: Hip (GS not reported)** Sensitivity: 85.5% Specificity: 92.6%	**FDG-PET: Knee (GS not reported)** Sensitivity: 94.4% Specificity: 79.2%	
Temmerman et al. 2007[20]	Plain radiography Subtraction arthrography Nuclear arthrography Bone scintigraphy Diagnosis of loose acetablular component of total hip prosthesis	Studies that evaluated diagnostic performance of any of the 4 imaging techniques in patients suspected of having loosening of a hip prosthesis. Minimum of 1-year follow-up or operation as a gold standard. Minimum of 10 patients. Sufficient data to determine sensitivity and specificity. Aseptic loosening only.	28	1975 to 2004	Modified Cochrane checklist used to generate a level of evidence ranging from 1 to 5, with "1" representing the highest level. All studies were rated a "4" due to lack of independent application of a reference standard or lack of blinding	**Subtraction arthrography (GS: operation)** Sensitivity: 89% (95% CI, 84% to 93%) Specificity: 76% (95% CI, 68% to 82%)	**Nuclear arthrography (GS: operation)** Sensitivity: 87% (95% CI, 57% to 97%) Specificity: 64% (95% CI, 40% to 82%)	**Bone scintigraphy (GS: operation)** Sensitivity: 67% (95% CI, 57% to 76%) Specificity: 75% (95% CI, 64% to 83%)

Table 7: Diagnostic Accuracy of Tests and Alternatives Based on the Information Presented in the Included Studies								
Study	**Tests and Indication**	**Study Eligibility**	**Number of Included Studies**	**Search**	**Quality of Included Studies**	**Diagnostic Accuracy versus Gold Standard**		
		Excluded reviews, abstracts, editorials, letters and comments.						
Prandini et al. 2006[21]	^{99m}Tc-WBCs ^{99m}Tc-BS ^{67}Ga scan FDG-PET ^{111}In-WBCs Diagnosis of bone infection due to peripheral open fractures or prosthetic joint implants	Included diagnostic studies of peripheral open fractures or prosthetic joint infections. Excluded papers regarding diabetic foot infections.	^{99m}Tc-WBCs — 22 ^{99m}Tc TPBS — 29 FDG-PET — 6 ^{111}In-WBCs — 26	1984 to 2004	Not reported	**^{99m}Tc-WBCs (HMPAO) (GS not reported)** Sensitivity: 89.0% Specificity: 89.1%	**^{99m}Tc-TPBS (GS not reported)** Sensitivity: 85.4% Specificity: 75.2%	**Alternate Tests (GS not reported)** FDG-PET Sensitivity: 94.1% Specificity: 87.3% ^{111}In-WBCs Sensitivity: 82.8% Specificity: 83.8%
Temmerman et al.	Plain radiography	Studies that evaluated diagnostic	Plain radiography — 17	1975 to 2004	Modified Cochrane checklist used	**Subtraction arthrography (GS: operation)**	**Nuclear arthrography (GS: operation)**	**Bone scintigraphy (GS: operation)**

Table 7: Diagnostic Accuracy of Tests and Alternatives Based on the Information Presented in the Included Studies								
Study	**Tests and Indication**	**Study Eligibility**	**Number of Included Studies**	**Search**	**Quality of Included Studies**	**Diagnostic Accuracy versus Gold Standard**		
2005[22]	Subtraction arthrography Nuclear arthrography Bone scintigraphy Diagnosis of aseptic loosening of femoral component of a hip prosthesis	performance of any of the 4 imaging techniques. Minimum of 1-year follow-up or operation as a gold standard. Minimum of 10 patients. Sufficient data to determine sensitivity and specificity. Excluded reviews, abstracts, editorials, letters and comments.	Subtraction arthrography — 9 Nuclear arthrography —10 Bone scintigraphy — 15		to generate a level of evidence ranging from 1 to 5, with "1" representing the highest level All studies were rated a "4" due to lack of independent application of a reference standard or lack of blinding	Sensitivity: 86% (95% CI, 74% to 93%) Specificity: 85% (95% CI, 77% to 91%)	Sensitivity: 85% (95% CI, 75% to 91%) Specificity: 83% (95% CI, 75% to 89%)	Sensitivity: 85% (95% CI, 79% to 89%) Specificity: 72% (95% CI, 64% to 79%)

BS = bone scan; CI = confidence interval; FDG = ^{18}fluorodeoxyglucose radiotracer; ^{67}Ga = gallium 67; GS = gold standard ; HMPAO = hexamethylpropyleneamine oxime; ^{111}In = Indium-111; MDP = methylene diphosphonate; NR = not reported; NS = not specified; PET = positron emission tomography; ^{99m}Tc = technetium-99m; TPBS = triple-phase bone scan; WBC = white blood cell

† Data not pooled ‡ Single study

APPENDIX 2.11

INDICATION OVERVIEW

Sudden cardiac arrest (SCA) is defined as an abrupt loss of consciousness and unexpected death (sudden cardiac death [SCD]) due to cardiac causes which occurs within one hour of symptom onset.[1] SCA is caused by ventricular arrhythmias, which are very rapid heartbeats that can lead to chaotic electrical heart activity resulting in death.[2] Eighty percent of SCA is attributed to ventricular tachycardia (VT) and ventricular fibrillation (VF).[1] Patients at risk for SCA may receive implantable cardioverter-defibrillators (ICDs). Individuals at the greatest risk for cardiac death are those with left ventricular (LV) dysfunctions. Nuclear imaging helps in determining cardiac blood flow, severity of disease, and therefore the likelihood for SCD from ischemia, which would benefit from revascularization (see ischemia section). Nuclear tests also evaluate LV function, which assists in determining if the patient is likely to benefit from an ICD.[3]

Population: Patients at risk for SCD who may benefit from an ICD.

Evidence from randomized clinical trials that confirmed the efficacy of ICD for primary and secondary prevention of SCD identified the populations who benefit from ICD. The benefits are restricted to those individuals with severe LV dysfunction as measured by ejection fraction (EF). The Canadian Cardiovascular Society (CCS) has published the following recommendations regarding the implantation of ICDs:[4,5]

- Referral for ICD therapy should be considered for patients with ischemic heart disease with or without mild to moderate heart failure symptoms and an LV ejection fraction of ≤ 30%, measured at least one month after myocardial infarction (MI) and at least three months following the coronary revascularization procedure.
- An ICD may be considered in patients with non-ischemic cardiomyopathy present for at least nine months, New York Heart Association (NYHA) functional class II to III heart failure, and an LV ejection fraction of ≤ to 30% or an LV ejection fraction of 31% to 35%.
- An ICD may be considered in patients with ischemic heart disease, previous myocardial infarction, LV dysfunction (LV ejection fraction 31% to 35%) measured at least one month after myocardial infarction and three months after coronary revascularization and with inducible ventricular fibrillation/sustained ventricular fibrillation/sustained ventricular tachycardia at electrophysiology study or without an electrophysiology study.
- An ICD should not be implanted in patients with poor life expectancy due to non-cardiac disease or NYHA class IV heart failure who are not expected to improve with further therapy and who are not candidates for cardiac transplantation.

Intervention: Radionuclide angiography (RNA) cardiac blood pooling imaging using ^{99m}Technetium (^{99m}Tc)-labelled radiotracer or gated single-photon emission computed tomography (SPECT) using ^{99m}Tc-labelled radiotracer.

Synonyms for RNA include radionuclide ventriculography, radionuclide cine angiography, gated blood pool, multiple gated acquisition scan, and equilibrium radionuclide angiography. The term RNA will be used throughout this report.

To perform RNA, red blood cells are labelled with ^{99m}Tc. Radioactivity is measured with a gamma camera suitably positioned over the patient's chest as the radioactive blood flows through the large vessels and heart. The number of counts recorded at any time is proportional to the amount of blood radioactivity and these counts are proportional to the LV volume.

The two methods used for measurement are first-pass and equilibrium RNA. First-pass RNA measures the radioactivity of only a few beats (usually six to 10) whereas equilibrium RNA accumulates data over a five- to 10-minute period. LV counts at end diastole and at end systole or throughout the cardiac cycle are measured by constructing an LV region of interest (ROI). The measured LV counts within these LV ROIs are corrected for background scatter (BkCorr). The left ventricular ejection fraction (LVEF) = ([BkCorr end-diastolic counts – BkCorr end systolic counts]/BkCorr end-diastolic counts) × 100.[6]

Comparators: For this report, the following diagnostic tests are considered as alternatives to RNA or ^{99m}Tc-labelled radiotracer red blood cell SPECT:

- *Echocardiography (Echo)*
- *Magnetic resonance imaging (MRI)*.

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 3) via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and implantable cardioverter-defibrillators.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. The search was limited to English language documents. No date limits were applied for the systematic reviews search. For primary studies, the retrieval was limited to documents published between January 1, 2006 and March 23, 2011. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

There were 40 potential clinical articles identified through the meta-analysis/systematic review/health technology assessment (MA/SR/HTA) filtered search and nine were subjected to full-text review. One systematic review and meta-analysis (2002)[7] is included in this report.

There were 345 potential articles identified through searching the primary diagnostic accuracy literature, of which 22 were subjected to full-text screening. Four primary studies, comparing RNA to its comparators, were identified in the primary literature search.[8-11] Three of the studies[8-10] evaluated RNA versus Echo and the fourth, also published in 2010,[11]compared RNA imaging with MRI in the determination of LVEF.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	The CCN's national ICD survey identified 29 sites across Canada where ICD implantation is done. Survey responses were received from 25 centres. The 25 centres indicated an annual ICD implant rate of 4,284 new and 1,582 replacement, for a total of 5,866 (Dan Purdham, Cardiac Care Network of Ontario; personal communication, February 23, 2012). The population of Canada in 2010 was 34,126,200, which indicates that more than 1.7 per 10,000 Canadians received ICDs that year. Given these estimates, and the understanding that cardiac imaging is conducted in order to determine eligibility for ICD implantation, the size of the affected population is estimated to be more than 1 in 10,000 (0.01%) and less than 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	According to the Wait Time Alliance, cardiac nuclear imaging for the evaluation of LV function should be performed within 24 hours for an emergency case (immediate danger to life, required for therapeutic management), within three days for urgent cases (situation is unstable and has the potential to deteriorate quickly and result in an emergency admission), or within 14 days for scheduled cases (situation involving minimal pain, dysfunction, or disability — also called "routine" or "elective").[12] For ICD decision-making purposes, the underlying condition has a significant impact on the management of the condition and the effective use of health care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	If the imaging test is not performed and the ICD-eligible patient does not receive an ICD, sudden death may occur.[13] Although no evidence was identified by the literature search to directly address this criterion, it is assumed that diagnostic imaging test results can have significant impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	If the imaging test is not done and the ICD-ineligible patient (LVEF is not less 35%) receives empirical ICD therapy, the patient is put at risk for ICD complications.[4] These complications include lead dislodgement, ICD system infection, pneumothorax, device malfunction, serious bleeding, venous thrombosis, and cardiac perforation.[4] Diagnostic imaging test results can have minimal impact on morbidity and quality of life.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	No information regarding acceptability of RNA by the patient was identified; however, with the assumption that the test is similar to other nuclear medicine tests, RNA is likely to be well-accepted. Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Echo is likely to be well tolerated by patients. Echo may be preferred by some patients, as there is no radiation exposure with it. Because of the closed space of MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[14,15] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. RNA imaging with ^{99m}Tc radiolabelled tracers is: • minimally less acceptable than Echo • minimally less acceptable than MRI.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
7	**Relative diagnostic accuracy of the test**	A 2002 meta-analysis by Ioannidis et al.[7] concluded that ECG-gated SPECT correlates well with cardiac MRI for measurement of LV volumes and EF. A 2010 primary study by Harel et al.[11] found that RNA provides good estimates of LVEF when compared with MRI as the gold standard. Three primary studies, published in 2010, evaluated ^{99m}Tc-RNA versus Echo. Lane et al.[8] intended to determine whether current screening techniques can identify patients who are deemed to be appropriate for ICD implantation. With Echo examined as the screening technique and RNA as the gold standard, the authors found the sensitivity of Echo for predicting an RNA LVEF < 30% to be 84.4% (specificity: 55.1%). Müller et al.[9] measured LVEF using real time 3-D Echo in a subset of patients with severe systolic dysfunction. Again, RNA was used as the reference standard. The correlation between Echo and RNA was described as modest (r = 0.49). Hutyra et al.[10] used gated cardiac SPECT as the reference standard in their evaluation of Echo. The correlation between the two modalities varied from 0.71 for monoplanar Echo to 0.88 for triplanar Echo. Based on the evidence available, the diagnostic accuracy of RNA imaging with ^{99m}Tc radiolabelled tracers: • is minimally better than Echo • has a similar diagnostic accuracy as MRI.
8	**Relative risks associated with the test**	**Non–radiation-related risks** No information was identified regarding the non–radiation-related risks for patients undergoing RNA. No risks associated with Echo were identified. MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[16] Side effects of Gd include headaches, nausea, and metallic taste. The frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%) and the frequency of moderate reactions range are also rare (0.004% to 0.7%).[17] **Radiation-related Risks** Patients undergoing RNA are exposed to a radiation dose of 6.2 mSv.[18] The comparators (Echo and MRI) do not expose the patient to ionizing radiation. Overall, RNA: • is minimally less safe than Echo • is minimally less safe than MRI.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
9	**Relative availability of personnel with expertise and experience required for the test**	*Expertise*: Sensitivity, specificity, and reproducibility of LVEF measures by Echo are strongly influenced by interobserver variability, whereas RNA is not. *Personnel*: In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic nuclear imaging, MRI, and U/S should be diagnostic radiologists or nuclear medical physicians. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). Not all radiologists, nuclear medical physicians, nuclear cardiologists, or cardiologists have the expertise to conduct ^{99m}Tc-RNA and all of its alternatives. For example, a 2002 report by the CCS reported that 43% of cardiologists do Echo. Assuming the necessary equipment is available, if ^{99m}Tc imaging using RNA is not available it is assumed that: • more than 95% of the procedures can be performed in a timely manner using Echo • 25-74% of the procedures can be performed in a timely manner using MRI.
10	**Accessibility of alternative tests (equipment and wait times)**	Nuclear medicine facilities with gamma cameras are required for RNA. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[19] SPECT/CT scanners were available in only five jurisdictions at that time: New Brunswick, Quebec, Ontario, Saskatchewan, and British Columbia.[19] No information was found to identify how many Echo machines are available in Canada. As of January 1, 2007, there were 6.8 MRI devices per million population in Canada, with no MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[19] According to the CIHI National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[19] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[20] Assuming the necessary expertise is available, if ^{99m}Tc imaging using RNA is not available it is estimated that: • more than 95% of the procedures can be performed in a timely manner using Echo • 25-74% of the procedures can be performed in a timely manner using MRI.
11	**Relative cost of the test**	According to our estimates, the cost of RNA with ^{99m}Tc-based radioisotopes is $330.40. Echo is a minimally less costly alternative, whereas MRI is moderately more costly than RNA with ^{99m}Tc-based radioisotopes.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**

Relative Costs

Test	Total Costs ($)	Cost of Test Relative to ^{99m}Tc-Based Test ($)
RNA	330.40	Reference
Echo	150.55	-179.85
MRI	759.29	+428.89

CCN = Cardiac Care Network; CCS = Canadian Cardiovascular Society; CIHI = Canadian Institute for Health Information; CT = computed tomography; 3-D = three-dimensional; ECG = electrocardiography; Echo = echocardiography; EF = ejection fraction; Gd = gadolinium; ICD = implantable cardioverter-defibrillator; LV = left ventricular; LVEF = left ventricular ejection fraction; MRI = magnetic resonance imaging; mSv = millisievert;PEI = Prince Edward Island; *r* = correlation coefficient; RNA = radionuclide angiography; SPECT = single-photon emission computed tomography; ^{99m}Tc = ^{99m}Technetium; U/S = ultrasound.

CRITERION 1: Size of affected population (link to definition)

The Cardiac Care Network of Ontario's national ICD survey identified 29 sites across Canada where ICD implantation is done. Survey responses were received from 25 centres. The 25 centres indicated an annual ICD implant rate of 4,284 new and 1,582 replacement, for a total of 5,866 (Dan Purdham, Cardiac Care Network of Ontario; personal communication, February 23, 2012). The population of Canada in 2010 was 34,126,200, which indicates that more than 1.7 per 10,000 Canadians received ICDs that year.

Given these estimates, and the understanding that cardiac imaging is conducted in order to determine eligibility for ICD implantation, the size of the affected population is estimated to be more than 1 in 10,000 (0.01%) and less than 1 in 1,000 (0.1%).

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

According to the Wait Time Alliance, cardiac nuclear imaging for the evaluation of LV function should be performed within 24 hours for an emergency case (immediate danger to life, required for therapeutic management), within three days for urgent cases (situation is unstable and has the potential to deteriorate quickly and result in an emergency admission), or within 14 days for scheduled cases (situation involving minimal pain, dysfunction, or disability — also called "routine" or "elective").[12]

For ICD decision-making purposes, the underlying condition has a significant impact on the management of the condition and the effective use of health care resources.

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Although no evidence was identified by the literature search to directly address this criterion, the assumption would be that patients who received an ICD would have lower mortality rates than those patients with similar cardiac functioning who did not receive an ICD. Patients with an LVEF less than 35% and previous occurrence of VF have the greatest benefit of reduced mortality from an ICD.[4] For primary prevention in high-risk patients with no previous occurrence of VF, the benefit is seen when LVEF is low (less than 30%).[4]

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

If the test is not done and the patient is not considered for an ICD, they may suffer SCD.[13]

If the test is not done and the patient receives an ICD based on clinical parameters, or empirically (and the LVEF is not less 35%), the patient has the potential of not achieving any clinical benefit from the ICD and may be exposed to potential complications. These complications include lead dislodgement, ICD system infection, pneumothorax, device malfunction, serious bleeding, venous thrombosis, and cardiac perforation.[4] In addition, some

ICD recipients will experience inappropriate shocks.[4] The occurrence of any shocks compared to no shocks is independently associated with statistically significant reductions ($P < 0.05$) in mental well-being and physical functioning in patients who received an ICD.[21]

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CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

RNA
No information regarding the acceptability of RNA by the patient was identified; however, with the assumption that the test is similar to other nuclear medicine tests, RNA is likely to be well-accepted. Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

Echo
This test is likely to be well-tolerated by patients. Echo may be preferred by some patients, as there is no radiation exposure.

MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise This may be less of a problem with new MRI machines, if available (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[14,15] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Systematic reviews and meta-analyses
One systematic review and meta-analysis (2002)[7] was identified in this report's meta-analysis/systematic review/health technology assessment (MA/SR/HTA).

^{99m}Tc-SPECT compared with MRI
Ioannidis et al. (2002)[7] performed a meta-analysis of all available data comparing electrocardiography(ECG)-gated SPECT with cardiac MRI in terms of the accurate assessment of LV and end-diastolic volumes, end-systolic volume, and EF. Data were eligible regardless of whether they referred to healthy subjects, patients with suspected or proven disease, and regardless of whether the SPECT images were captured at rest or after stress. All technical parameters and algorithms used for LV volumes and EF calculations were included. Only the ^{99m}Tc data were pooled in the analysis.

Nine studies were included in the analysis (164 subjects who had both a ^{99m}Tc-SPECT and MRI scan). Study populations included: known or suspected coronary artery disease (n = 5), post-MI (n = 1), post-coronary artery bypass grafting (n = 1), normal EF (n = 1), EF < 40% (n = 1), mixed (SPECT referrals, n = 1). All studies used rest acquisitions. Seven studies reported that test interpretation was blinded to the results of the other test. Sensitivity and specificity were calculated for each study and pooled using simple pooling techniques. In cases of significant heterogeneity, random effects analysis was used (Table 2).

Table 2: Diagnostic Accuracy Characteristics for EF Measurements of ^{99m}Tc-SPECT Using MRI as the Gold Standard

Simple Pooling for Detecting EF ≤ 40%	
Sensitivity	91% (95% CI, 80% to 97%)
Specificity	88% (95% CI, 80% to 93%)
Random Effects Pooling for Detecting EF ≤ 40%	
Sensitivity	83% (95% CI, 69% to 92%)
Specificity	84% (95% CI, 75% to 90%)
Overall correlation coefficient	0.90, P < 0.001
Discrepancies Between EF Measures	
≥ 5%	52% (95% CI, 37% to 63%)
≥ 10%	23% (95% CI, 11% to 42%)

CI= confidence interval; EF = ejection fraction; MRI = magnetic resonance imaging; MRI = magnetic resonance imaging; ^{99m}Tc-SPECT = ^{99m}technetium-single photon emission computed tomography.

Primary Studies

Four primary studies comparing RNA to its comparators were identified in the primary literature search.[8-11] Three of the studies[8-10] evaluated RNA versus Echo and the fourth, also published in 2010,[11] compared RNA imaging to MRI in the determination of LVEF.

^{99m}Tc-RNA versus Echo

An important Canadian study by Lane et al. (2010)[8] examined the usefulness of current screening techniques using Echo to identify patients who should receive a primary prophylactic ICD. Two-hundred and forty-one patients, seen for consideration for a primary prophylactic defibrillator and referred for both Echo and RNA, were included in the analysis.[8] The screening Echo used semi-quantitative or quantitative methods to measure the LVEF.[8] In Table 3 and 3A, Echo grade 3 refers to LVEF of 20% to 39%, and Echo grade 4 refers to LVEF of < 20%.[8] The study authors concluded that Echo and RNA are not equivalent modalities for measuring LVEF.[8]

Table 3: Semi-quantitative Echo Diagnostic Criteria for Screening LVEF[8]

Echo Grade	Sensitivity (%)	Specificity (%)	Positive Likelihood Ratio	Negative Likelihood Ratio	Positive Predictive Value (%)	Negative Predictive Value (%)
RNA LVEF < 30%						
4	40.9	85.5	2.83	0.69	78.9	52.2
3 to 4 or worse	58.2	65.1	1.67	0.64	68.8	54.0
3 or worse	95.5	21.7	1.22	0.21	61.8	78.3

Table 3: Semi-quantitative Echo Diagnostic Criteria for Screening LVEF[8]						
Echo Grade	**Sensitivity (%)**	**Specificity (%)**	**Positive Likelihood Ratio**	**Negative Likelihood Ratio**	**Positive Predictive Value (%)**	**Negative Predictive Value (%)**
RNA LVEF < 35%						
4	34.6	90.0	3.46	0.73	93.0	26.5
3 to 4 or worse	52.9	70.0	1.76	0.67	87.1	28.0
3 or worse	92.8	30.0	1.33	0.24	83.5	52.2

Echo = echocardiography; LVEF = left ventricular ejection fraction; RNA = radionuclide angiography.

Table 3A: Quantitative Echo for Screening LVEF[8]				
	Sensitivity (%)	**Specificity (%)**	**Positive Likelihood Ratio**	**Negative Likelihood Ratio**
RNA LVEF < 30%	84.4	55.1	1.88	0.28
RNA LVEF < 35%	88.7	48.2	1.71	0.23

Echo = echocardiography; LVEF= left ventricular ejection fraction; RNA= radionuclide angiography.

Müller et al. (2010)[9] compared LVEF measures between RNA and three-dimensional (3-D) Echo. Consecutive patients sent to their facility with an LVEF < 35% measured visually by two-dimensional Echo underwent a full-volume 3-D Echo and an RNA one week later. All images were interpreted blindly. Fifty patients were enrolled: 58% with ischemic heart disease, and 42% with dilated cardiomyopathy. Only 38 patients (76%) had Echo images of sufficient quality for evaluation. The study authors concluded that RNA and 3-D Echo are not interchangeable for LVEF measures in patients with severely depressed systolic function.

Table 4: LVEF measures for 3-D Echo and RNA				
	Mean LVEF (SD)		**Mean Difference (SD) (Echo — RNA)**	**Agreement (95% limits)**
	RNA	**3-D Echo**		
All patients (n = 50)	0.27 (0.09)	0.20 (0.07)*	–0.07 (0.09)	–0.24 to 0.10
Only good quality images (n = 38)	0.27 (0.08)	0.21 (0.07)*	–0.05 (0.07)	–0.20 to 0.09

3-D = three-dimensional; Echo = echocardiography; LVEF = left ventricular ejection fraction; RNA = angiography; SD = standard deviation

*=statistically significantly smaller values, p<0.001

In a 2010 publication by Hutyra et al., a cohort (n = 70) of ischemic cardiomyopathy patients underwent both Echo (monoplane and two-dimensional) and ^{99m}Tc sestamibi-labelled SPECT scans to measure LVEF.[10] SPECT scans were followed by Echo one hour later. ^{99m}Tc-SPECT EFs were obtained using software. Single-measured Echo parameters were triplanar, biplanar, and monoplanar, and images were interpreted blindly. Patients with ischemic cardiomyopathy indicated for cardiosurgical revascularization based on coronarography were evaluated. All patients were New York Heart Association (NYHA) I-III and 65% had verified LV systolic dysfunction defined by LVEF < 50%. As indicated in Table 5, ^{99m}Tc-SPECT and Echo LVEF measurements were significantly correlated, with the best agreement seen with triplanar Echo.

The study authors concluded that, for a one-time measurement, two-dimensional Echo using the triplanar analysis is interchangeable with ^{99m}Tc-SPECT.

Table 5: Diagnostic Parameters of Echo and SPECT[10]

Scan	LVEF (SD)	Median LVEF diff (95% CI)	Correlation Coefficient	Agreement (95% Lower & Upper Limits)
^{99m}Tc-SPECT	36.6% (11.5%)	Reference	Reference	N/A
Echo –monoplanar	36.6% (12.2%)	0.1% (–1.9 to –2.1)	0.71*	–0.8% (–17.2 to 17.3)
Echo – biplanar	35.7% (10.0%)	0.7% (–0.5 to –2.5)	0.83*	–0.7% (–13.4 to 11.7)
Echo – triplanar	35.9% (10.0)	0.4% (–0.7 to –1.7)	0.88*	–0.4% (–11.7 to 10.7)

CI = confidence interval; diff = difference; Echo = echocardiography; LVEF = left ventricular ejection fraction; N/A = not applicable; SD = standard deviation; SPECT = single-photon emission computed tomography; ^{99m}Tc-SPECT = ^{99m}technetium single-photon emission computed tomography.
*P value < 0.001.

^{99m}Tc-RNA versus MRI

Harel et al.[11] evaluated the use of a radionuclide-gated blood pool SPECT algorithm and cardiac MRI, with a study population of 55 patients. The mean delay between the two imaging tests was 12 ± 10 days. The mean LVEF estimates estimated by the different imaging modalities and algorithms are provided in Table 6. LVEFs calculated with planar, MHI_{space}, and QBS_{space} methods were correlated with LVEF values obtained by cardiac MRI. Count-based algorithms provided increased correlation. The authors concluded that RNA provided good estimates of LVEF when compared to cardiac MRI as the gold standard.

Table 6: Left Ventricular Ejection Fraction (LVEF) Estimates

Test	Mean LVEF ± SD (%)	Correlation Coefficient
cMRI (gold standard)	39 ±13	n/a
Planar RNA	40 ± 13	0.81
MHI_{space}	43 ± 12	0.82
QBS_{space}	39 ± 14	0.82
MHI_{count}	42 ± 13	0.88
QBS_{count}	46 ± 15	0.84

cMRI = cardiac magnetic resonance imaging; LVEF = left ventricular ejection fraction; MHI = Montreal Heart Institute blood-pool software; QBS = quantitative blood-pool software (Cedar-Sinai); RNA = radionuclide angiography; SD = standard deviation.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

RNA

No information was identified regarding non–radiation-related risks for patients.

Echo

Three relatively large studies — with sample sizes of 42,408 patients (2009),[22] 26,774 patients (2009),[23] and 5069 patients (2008)[24] — compared cardiac outcomes (non-fatal MI or death) between patients who underwent contrast-enhanced Echo with patients who had an Echo without contrast. All three studies concluded that the risk of an adverse event is low and is no different than that of patients who received no contrast. No additional risks associated with Echo were identified.

MRI
MRI is contraindicated in patients with metallic implants including pacemakers.[25] MRI is often used in conjunction with the contrast agent gadolinium (Gd). Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[16] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[17] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[17]

Radiation-related Risks

Among the modalities to assess chemotherapy-induced cardiotoxicity, RNA is the only one to expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 7.

Table 7: Effective Radiation Doses for Various Imaging Tests

Test	Effective Radiation Dose (mSv)
RNA	6.2[18]
Average background dose of radiation per year	1 to 3.0[26-28]

mSv = millisievert ; RNA = radionuclide angiography.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to make decisions regarding ICD implantation are presented by imaging modality. A summary of the availability of personnel required for ICD decision-making, by RNA or any of the alternative imaging modalities, is provided in Table 8.

RNA
In Canada, physicians involved in the performance, supervision, and interpretation of cardiac nuclear imaging (specifically RNA using ^{99m}Tc-labelled radiotracer) should be nuclear medicine physicians with particular expertise in nuclear cardiology. In some jurisdictions, cardiologists also provide much of the nuclear cardiology services. According to the Canadian Medical Association (CMA), there are 1,149 practising cardiologists in Canada (CMA, 2011).

Nuclear medicine technologists are required to conduct RNA scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound should be diagnostic radiologists[19] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists are also qualified if they are certified by a recognized certifying body and hold a valid provincial licence.[29] According to the CMA, there are 1,149 practising cardiologists in Canada (CMA, 2011).

Medical radiation technologists must be certified by CAMRT or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on-site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, MRI scanners, and nuclear medicine equipment.[29]

Echo
Echocardiography is an ultrasound-based test. Cardiologists provide much of the Echo service. A 2002 report by the CCS reported that 43% of cardiologists do Echo. According to the CMA, there are 1,149 practising cardiologists in Canada (CMA, 2011). It is assumed that less than 500 of them do Echo.

Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals (CARDUP). They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[19] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[19]

MRI
Medical technologists must have CAMRT certification in magnetic resonance imaging or be certified by an equivalent licensing body recognized by CAMRT.

Table 8: Medical Imaging Professionals in Canada, 2006[19]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	MRTs	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRT = medical radiation technologist; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; ON = Ontario; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 9 provides an overview of the availability of equipment required to make decisions regarding ICD implantation. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of MRI and SPECT/CT scanners is current to January 1, 2010. Data were not available for Echo.

Table 9: Diagnostic Imaging Equipment in Canada[19,30]

	Nuclear Medicine Cameras	MRI Scanners	SPECT/CT Scanners
Number of devices[19,30]	603[19]	218[30]	96[30]
Average number of hours of operation per week (2006-2007)[19]	40	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	YT, NT, NU	PEI, YT, NT, NU

CT = computed tomography; MRI = magnetic resonance imaging; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; SPECT = single-photon emission computed tomography; YT = Yukon.

RNA
Nuclear medicine facilities with gamma cameras are required for SPECT imaging. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[19]

Echo
No information was found to identify how many Echo machines are available in Canada.

MRI
No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[30] According to the Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[19] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[20]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of RNA and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 10), the cost of RNA with ^{99m}Tc-based radioisotopes is $330.40. Echo is a minimally less costly alternative, whereas MRI is moderately more costly than RNA with ^{99m}Tc-based radioisotopes.

Table 10: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[31]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
RNA				
J813	Myocardial wall motion — studies with ejection fraction	138.60	82.25	220.85
J866	Application of SPECT (maximum 1 per examination)	44.60	31.10	75.70
Maintenance fees — from global budget		33.85		33.85
	TOTAL	217.05	113.35	**330.40**
Echo				
G570/G571	Complete study — 1 and 2 dimensions	76.45	74.10	150.55
	TOTAL	76.45	74.10	**150.55**
MRI				
X441C	MRI — thorax — multislice sequence		77.20	115.85
X445C (×3)	Repeat (another plane, different pulse sequence — to a maximum of 3 repeats)		38.65 (×3) = 115.95	115.95
X499	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40
X487	When gadolinium is used		38.60	38.60
X486	When cardiac gating is performed (must include application of chest electrodes and ECG interpretation), add 30%		89.14	89.14
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	373.00	386.29	**759.29**

3-D = three-dimensional; ECG = electrocardiogram; Echo = echocardiogram; MRI = magnetic resonance imaging; prof. = professional; RNA = radionuclide angiogram; SPECT = single-photon emission computed tomography; tech. = technical.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE <1946 to March 23, 2011>
Date of Search:	March 23, 2011
Alerts:	Monthly search updates began March 23, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	English language No date limits for systematic reviews Publication years 2006-2011 for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Multi-database Strategy	
#	**Searches**
1	Defibrillators, Implantable/
2	((Implant* or internal) adj5 (defibrillator* or cardioverter* or cardioversion)).ti,ab.
3	(ICD or ICDs).ti,ab.
4	Ventricular Dysfunction, Left/ri
5	or/1-4
6	Ventricular Dysfunction, Left/
7	(left ventricular ejection fraction or LVEF or left ventricular dysfunction).ti,ab.
8	1 or 2 or 3 or 6 or 7

Multi-database Strategy	
9	Technetium/
10	exp Technetium Compounds/
11	exp Organotechnetium Compounds/
12	exp Radiopharmaceuticals/
13	(Technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc*).tw,nm.
14	Radionuclide Imaging/ or Perfusion Imaging/
15	radionuclide imaging.fs.
16	radioisotope*.mp.
17	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
18	exp Tomography, Emission-Computed, Single-Photon/
19	(single-photon adj2 emission*).ti,ab.
20	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
21	exp Tomography, Emission-Computed, Single-Photon/
22	Radionuclide Angiography/
23	exp Radionuclide Ventriculography/ or Gated Blood-Pool Imaging/ or Cardiac-Gated Imaging Techniques/
24	((gated or gate) adj2 (blood pool or acquisition)).ti,ab.
25	RNA.ti,ab.
26	((radionuclide or nuclear) adj2 (ventriculograph* or angiograph* or angiocardiograph*)).ti,ab.
27	(RNA or RNCA or ERNA).ti,ab.
28	or/9-27
29	meta-analysis.pt.
30	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
31	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
32	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
33	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
34	(data synthes* or data extraction* or data abstraction*).ti,ab.
35	(handsearch* or hand search*).ti,ab.
36	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
37	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
38	(meta regression* or metaregression* or mega regression*).ti,ab.
39	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
40	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
41	(cochrane or health technology assessment or evidence report).jw.
42	or/29-41
43	8 and 28 and 42
44	43
45	limit 44 to english language
46	exp "Sensitivity and Specificity"/

Multi-database Strategy	
47	False Positive Reactions/
48	False Negative Reactions/
49	du.fs.
50	sensitivit*.tw.
51	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti,ab.
52	(predictive adj4 value*).tw.
53	Comparative Study.pt.
54	(Validation Studies or Evaluation Studies).pt.
55	Randomized Controlled Trial.pt.
56	Controlled Clinical Trial.pt.
57	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
58	Multicenter Study.pt.
59	(random* or sham or placebo*).ti.
60	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
61	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
62	(control* adj3 (study or studies or trial*)).ti.
63	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
64	(allocated adj "to").ti,ab.
65	Cohort Studies/
66	Longitudinal Studies/
67	Prospective Studies/
68	Follow-Up Studies/
69	Retrospective Studies/
70	Case-Control Studies/
71	Cross-Sectional Study/
72	(observational adj3 (study or studies or design or analysis or analyses)).ti.
73	cohort.ti.
74	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
75	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
76	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
77	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
78	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
79	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
80	(population adj3 (study or studies or analysis or analyses)).ti.
81	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
82	or/46-81
83	82 not case reports.pt.
84	5 and 28 and 83
85	84
86	limit 85 to (english language and yr="2006 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 3, 2011;	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 21-25, 2011
Keywords:	Included terms for implantable cardioverter-defibrillators and radionuclide imaging
Limits:	English language

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http:www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

APPENDIX 2.12

INDICATION OVERVIEW

Acute cholecystitis is a sudden onset of inflammation of the gallbladder that causes severe abdominal pain. Abdominal pain is often accompanied by fever and abnormally high white blood cell count (leukocytes).[1] Acute cholecystitis is usually caused by gallstones obstructing the cystic duct.[2] This prevents the normal flow of bile in and out of the gallbladder into the bowel. Increased pressure in the gallbladder due to the obstruction results in inflammation and pain. Up to 14% of acute cholecystitis cases are acalculous.[2] In these patients, there is an obstruction but gallstones are not the cause. Acute acalculous cholecystitis usually occurs in patients who are already critically ill from another medical condition. Mortality and morbidity is high in patients with acute acalculous cholecystitis.

The initial treatment for acute cholecystitis in the emergency room is usually intravenous antibiotics, hydration, and analgesia. If inflammation of the gallbladder continues, removal of the gallbladder (cholecystectomy) is usually required.[3]

Complications of acute cholecystitis include gangrenous cholecystitis (gangrene of the gallbladder wall), gallbladder perforation (hole or piercing of the wall of the gallbladder), and emphysematous cholecystitis (acute infection of the gallbladder caused by gas-forming organisms). These complications occur in up to 20% of people with cholecystitis, have high mortality associated with them, and therefore require emergency surgery.[2]

Population: Patients with suspected acute cholecystitis.

Intervention: Cholescintigraphy.

Cholescintigraphy, also known as a hepatobiliary iminodiacetic (HIDA) scan, is a nuclear medicine test used to diagnose intrahepatic or extrahepatic obstruction of the bile ducts, gallbladder disease, and bile leaks. Before cholescintigraphy, patients are injected with a radiopharmaceutical tracer (technetium-99m [^{99m}Tc]-iminodiacetic acid). Patients need to fast three to four hours before this injection to avoid gallbladder contraction.[4] After injection, a gamma camera is used to detect gamma rays emitted by the patient from the injected radiopharmaceuticals. Images are created from the detected gamma rays. If there is no cystic duct blockage, the radiopharmaceutical will enter the gallbladder, which will be visualized in images created by the gamma camera. If a gallstone is obstructing a patient's cystic duct, the radiopharmaceutical will not enter the gallbladder and visualization of the gallbladder cannot occur. Non-visualization of the gallbladder is indicative of acute cholecystitis. If the gallbladder is not seen one hour after injection, images should be retaken three to four hours after injection.[5] This delayed imaging increases the specificity of cholescintigraphy for the diagnosis of acute cholecystitis. An alternative to delayed imaging is to inject the patient with a small amount of morphine sulphate (0.02 mcg/kg). Administration of morphine sulphate facilitates the flow of bile toward the cystic duct by causing contraction of the sphincter of Oddi. The injection of morphine sulphate can reduce the time to confirm the diagnosis from three or four hours to 1.5 hours.[4]

Comparators: For this report, the following diagnostic tests are considered as alternatives to cholescintigraphy:

- *Computed Tomography (CT):* In a CT scan, a rotating x-ray device moves around the patient and takes multiple detailed images of organs and body parts.[6] Sometimes patients are injected with a contrast agent before images are taken, for better visualization of the body part being examined.[6] CT findings consistent with acute cholecystitis include gallbladder wall thickening, gallbladder distention, pericholecystic fluid, and pericholecystic fat.
- *Magnetic Resonance Cholangiopancreatography (MRCP):* An MRCP is a magnetic resonance imaging (MRI) test that produces detailed images of the hepatobiliary and pancreatic systems. Images are created using a magnetic field and radiofrequency pulses. Patients undergoing MRI are placed on to a table that is moved into the centre of the MRI machine. Some patients are given contrast material before the MRI. MRCP findings indicative of acute cholecystitis include gallbladder stones, wall thickening, and pericholecystic fluid.[7]
- *Ultrasound (U/S):* During a U/S, a transducer is placed over the organ of interest. The transducer generates sound waves that pass through the body and produce echoes that are analyzed by a computer to produce images of the body part being analyzed.[8] U/S findings consistent with acute cholecystitis include the visualization of gallstones, intraluminal sludge, thickening of the gallbladder wall, pericholecystic fluid, increased blood flow in the gallbladder wall, and sonographic Murphy's sign.[9] Murphy's sign of cholecystitis refers to pain felt by the patient on taking a deep breath while pressure is placed in the right upper quadrant of the abdomen.[10]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 2) via Wiley; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and cholecystitis.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. The search was limited to English language. No date limits were applied for the systematic review search. The primary studies search was limited to documents published between January 1, 1996, and March 2, 2011. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

Fourteen articles[11-24] were identified through the MA/SR/HTA search; of those, eight[13-18,21,24] underwent full text review. One systematic review[15] was identified from the full text review that compared the diagnostic accuracy of cholescintigraphy with one of the alternative imaging modalities.

A review of primary studies was conducted to identify studies that directly compared the diagnostic accuracy of cholescintigraphy with one of its alternatives. Four primary studies[25-28] were found that compared cholescintigraphy with U/S. No primary studies were identified that directly compared cholescintigraphy with CT, with MRCP, or with ERCP. Articles from the grey literature search were used to address criterion 1 (one article)[29] and criterion 8 (one article).[30] Articles from the primary study search were used to help address criterion 1 (one article),[31] criterion 3 (one article),[32] criterion 6 (four articles), and criterion 8 (two articles).

Literature from targeted searches was used to supplement the articles identified in the primary study search. When no literature was identified addressing specific criteria, experts were consulted.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	No estimates of point prevalence of acute cholecystitis were found in the literature. An Ontario hospital-based study[29] estimated the annual incidence of acute cholecystitis from 1992 to 2000 to be 0.88 people per 1,000 population. The size of affected population is more than 1 in 10,000 (0.01%) and less than or equal 1 in 1,000 (0.1%)
2	**Timeliness and urgency of test results in planning patient management**	Saskatchewan hospital guidelines indicate that cholescintigraphy for diagnosis of suspected acute cholecystitis should be conducted within 24 hours (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011) The target time frame for performing the test is in 24 hours or less and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has significant impact on the management of the condition or the effective use of health care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	If a test for diagnosing acute cholecystitis is not available, treatment might be delayed and complications associated with high mortality rates might be more likely to develop. Complications from acute cholecystitis occur in around 20% of patients and complicated acute cholecystitis is associated with a mortality rate of around 25%.[33] Perforation of the gallbladder, which occurs in 3% to 15% of patients with cholecystitis, has a 60% mortality rate.[34] Acute acalculous cholecystitis has a mortality rate of around 30%.[35] Diagnostic imaging test results can have minimal impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	If a test for diagnosing acute cholecystitis is not available, treatment might be delayed and patients may have to suffer symptoms of acute cholecystitis longer than necessary. Delayed treatment will make patients more susceptible to complications that could increase the global hospitalization length and have an impact on their survival or quality of life. Diagnostic imaging test results can have moderate impact on morbidity or quality of life.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on**	To be scored locally.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
	health disparities	
6	**Relative acceptability of the test to patients**	*Cholescintigraphy* Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. *CT* Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion). Patients may be required to hold their breath for a substantial period of time, which is seen as "uncomfortable" and "difficult," particularly for patients with severe abdominal pain.[36] *MRCP* MRCP is an MRI-based imaging test. Because of the closed space of an MRI, patients may experience feelings of claustrophobia as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[37,38] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. *U/S* Some discomforts associated with U/S include cold, unspecified pain, and tenderness. In a study comparing U/S with MRI in undiagnosed shoulder pain, 100% of the patients participating said that they would be willing to undergo the U/S exam again.[39] This test may be preferred in pediatric patients as there is no exposure to ionizing radiation, and the test does not require sedation. Overall, acceptability to patients of cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is: • minimally more acceptable than CT • minimally less acceptable than MRCP, • minimally less acceptable than U/S.
7	**Relative diagnostic accuracy of the test**	*Cholescintigraphy versus U/S* The table presents the sensitivity and specificity reported in one systematic review[15] and three primary studies[25,27,28] that compared the diagnostic accuracy of cholescintigraphy and U/S for acute cholecystitis. Diagnosis of acute cholecystitis was confirmed with pathological or surgical

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>findings (gold standard).
<table>
<tr><th colspan="7">Diagnostic Accuracy</th></tr>
<tr><th rowspan="2">Author, Year</th><th colspan="3">Cholescintigraphy</th><th colspan="3">U/S</th></tr>
<tr><th>N</th><th>Sensitivity</th><th>Specificity</th><th>N</th><th>Sensitivity</th><th>Specificity</th></tr>
<tr><td>Shea et al. 1994[15]</td><td>2466</td><td>0.97</td><td>0.90</td><td>532</td><td>0.88</td><td>0.80</td></tr>
<tr><td>Chatziioannou et al. 2000[27]</td><td>107</td><td>0.88</td><td>0.93</td><td>107</td><td>0.50</td><td>0.88</td></tr>
<tr><td>Kalimi et al. 2001[28]</td><td>28</td><td>0.86</td><td>NR</td><td>50</td><td>0.48</td><td>NR</td></tr>
<tr><td>Alobaidi et al. 2004[25]</td><td>22</td><td>0.91</td><td>NR</td><td>100</td><td>0.62</td><td>NR</td></tr>
</table>
N = number of patients; U/S = ultrasound.

Cholescintigraphy versus CT
No studies comparing the diagnostic accuracy of cholescintigraphy and CT for acute cholecystitis were identified.

Cholescintigraphy versus MRCP
No studies comparing the diagnostic accuracy of cholescintigraphy and MRCP for acute cholecystitis were identified.

Based on limited evidence and expert opinion, the diagnostic accuracy of cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is:

moderately better than CT
similar to MRCP,
minimally better than U/S.
</td></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>Non–radiation-related Risks

Cholescintigraphy
Risks associated with a cholescintigraphy include allergy to HIDA and pain during CCK injection (causes gallbladder contraction), chills, nausea, and rash.[40]

CT</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses	
Criterion	**Synthesized Information**

Some patients may experience an allergic reaction to the contrast agent (if required).[41] In addition, patients may experience mild side effects from the contrast agent, such as nausea, vomiting, or hives. A 2009 retrospective review of 456,930 intravascular doses of low-osmolar iodinated and Gd contrast materials administered between 2002 and 2006 found 0.15% of patients experienced side effects, most of which were mild. According to the American College of Radiology *Manual on Contrast Media,*[42] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%).

MRCP

MRCP is an MRI-based test and is contraindicated in patients with metallic implants, including pacemakers.[43] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required).[41] Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. The frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%).[42]

U/S

There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

Some tests expose patients to radiation. The following table presents the effective radiation dose to which patients are exposed during the various diagnostic tests.

Radiation doses	
Test	**Effective Radiation Dose (mSv)**
Cholescintigraphy	3.1[44]
Abdominal CT	8.0[44]
MRCP (MRI)	0[30]
Abdominal U/S	0[30]
Annual natural radiation exposure	1 to 3.0[44-46]

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		Overall, the risks associated with cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is: • minimally safer than CT • minimally less safe than MRCP, • minimally less safe than U/S.
9	**Relative availability of personnel with expertise and experience required for the test**	As of 2006 in Canada, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, 1,781 nuclear medicine technologists, and 2,900 sonographers available across Canada. Yukon, Northwest Territories, and Nunavut do not have the available personnel to perform and interpret tests to detect bile leak. Other jurisdictions (e.g., Prince Edward Island) may offer limited nuclear medicine services. Assuming the necessary equipment is available, if cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using CT • 25-74% of the procedures can be performed in a timely manner using MRCP • more than 95% of the procedures can be performed in a timely manner using U/S.
10	**Accessibility of alternative tests (equipment and wait times)**	*Cholescintigraphy* For the diagnosis of acute cholecystitis, nuclear medicine facilities with gamma cameras (including SPECT) are required. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[47] *MRCP* No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[48] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006-2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario with a national average of 71 hours.[47] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[49] *CT* No CT scanners are available in Nunavut.[48] For CT scanners, the average weekly use ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[47] *U/S*

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>The median wait time for a U/S in Canada was estimated to be 4.5 weeks in 2010.[49] No information was found on the number of U/S machines available in Canada.

Assuming the necessary expertise is available, if cholescintigraphy using ^{99m}Tc-radiolabelled isotopes is not available, it is estimated that:
more than 95% of the procedures can be performed in a timely manner using CT
25-74% of the procedure can be performed in a timely manner using MRCP,
more than 95% of the procedures can be performed in a timely manner using U/S.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of cholescintigraphy with ^{99m}Tc-based radioisotopes is $298.38. CT is minimally more costly and MRCP is moderately more costly. U/S is minimally less costly.

<table>
<tr><th colspan="3">Relative costs</th></tr>
<tr><th>Test</th><th>Total costs ($)</th><th>Cost of test relative to ^{99m}Tc-based test ($)</th></tr>
<tr><td>Cholescintigraphy</td><td>298.38</td><td>Reference</td></tr>
<tr><td>CT</td><td>383.85</td><td>+85.47</td></tr>
<tr><td>MRCP</td><td>595.15</td><td>+296.77</td></tr>
<tr><td>U/S</td><td>88.25</td><td>-210.13</td></tr>
</table>
</td></tr>
</table>

CCK = cholecystokinin; CIHI = Canadian Institute for Health Information; CT = computed tomography; Gd = Gadolinium; HIDA = hepatobiliary iminodiacetic acid; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; mSv = millisievert; NR = not reported; SPECT = single-photon emission computed tomography; ^{99m}Tc = technetium-99m; U/S = ultrasound.

CRITERION 1: Size of affected population (link to definition)

No estimates of point prevalence of acute cholecystitis were found in the literature. An Ontario study that estimated the annual incidence of acute cholecystitis was identified.[29] Urbach and Stukel[29] sought to find out whether the observed increased rate of elective cholecystectomy resulted in changes in the incidence of severe complications of gallbladder disease, including acute cholecystitis. Cases of severe gallbladder complications occurring from 1988 through 2000 in persons aged 18 years and older in Ontario were identified from hospital admission data from the Canadian Institute of Health Information (CIHI) and the Ontario Health Insurance Plan. Hospital admissions for acute cholecystitis were identified using specific ICD-9-CM codes. The authors estimated the average annual incidence rate of acute cholecystitis in Ontario during the years 1992-2000 to be 88.1 per 100,000 people. This is equivalent to 0.88 people per 1,000 people.

No other estimates of the prevalence or incidence of acute cholecystitis were found in the literature search. However, estimates of the prevalence of gallstones, the primary cause of acute cholecystitis, were found. It has been estimated that up to 10% to 20% of residents of the United States have gallstones and that one-third of these patients will suffer from acute cholecystitis at some point in their lives.[31]

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Saskatchewan hospital guidelines indicate that cholescintigraphy for diagnosis of suspected acute cholecystitis should be conducted within 24 hours (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011).

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

If a test for diagnosing acute cholecystitis is not available, treatment might be delayed and complications with associated high mortality rates might be more likely to develop. Complications from acute cholecystitis occur in around 20% of patients. Complicated acute cholecystitis is associated with a mortality rate of around 25%.[33] Perforation of the gallbladder, which occurs in 3% to 15% of patients with cholecystitis, has a 60% mortality rate.[34] Acute acalculous cholecystitis has a mortality rate of around 30%.[35]

In an analysis of more than 29,000 elderly Medicare beneficiaries who presented with acute cholecystitis, those who were immediately treated with cholecystectomy had a lower mortality rate than patients not immediately treated with cholecystectomy.[34,50] Patients given immediate cholecystectomy had mortality rates of 2.0%, 9.5%, and 15.2% at 30 days, one year, and two years, respectively. Patients not immediately treated with cholecystectomy had mortality rates of 5.0%, 19.4%, and 29.3% at 30 days, one year, and two years, respectively.

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

If a test for diagnosing acute cholecystitis is not available, treatment might be delayed and patients may have to suffer symptoms of acute cholecystitis longer than necessary. Additionally, delayed treatment may make patients more susceptible to complications that could affect their survival or their quality of life.

Two studies were identified that evaluated the quality of life impact of acute cholecystitis. A 2005 Norwegian study by Vetrhus et al.[51] compared the quality of life over a five-year period of 64 patients presenting at their institution with acute cholecystitis. Patients were randomized to one of two treatment groups (all patients treated conservatively with antibiotics): observation, or cholecystectomy. Quality of life was assessed using the Psychological General Well-Being index (PGWB) and the Nottingham Health Profile (NHP) part II. Pain was evaluated using a pain score and a visual analogue pain scale (VAPS). No statistically significant differences between the two treatment groups over time were found in any of the instruments. However, the differences in mean scores in the quality of life and pain instruments at randomization and at five years reflect the morbidity impact of the acute cholecystitis episode. Table 2 presents selected findings of the study.

Table 2: Selected Results Reported in Vetrhus et al. 2005[51]

Instrument	Mean Score		Interpretation
	Randomization	5 years	
PGWB			Higher scores reflect better quality of life
Observation	94.2	112.0	
Cholecystectomy	88.1	102.5	
NHP			Higher scores reflect worse quality of life
Observation	2.0	0.7	
Cholecystectomy	2.2	1.4	
Pain Score			Higher scores reflect worse pain
Observation	6.6	1.3	
Cholecystectomy	8.1	2.6	
VAPS			Higher scores reflect worse pain
Observation	57.1	6.2	
Cholecystectomy	57.7	11.3	

NHP = Nottingham Health Profile part II; PGWB = Psychological General Well-Being index; VAPS = visual analogue pain scale.

Bass et al.[52] estimated the quality of life impact of different types and treatments of gallbladder disease. After being presented with descriptions of different diseases and procedures, 40 subjects (without gallstones) provided preference scores by means of either a simple 0 to 100 rating scale (n = 22; score of 0 = immediate death and 100 = perfect health) or standard gamble (n = 18). The relative mean rating score — rated relative to other related conditions — for an episode of acute cholecystitis was 0.36 and 0.77 by standard gamble.

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CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

Cholescintigraphy
Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

CT
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner. This is less of a problem with new CT scanners (MIIMAC expert opinion). Patients may be required to hold their breath for a substantial period of time, which is seen as "uncomfortable" and "difficult," particularly for patients with severe abdominal pain.[36]

MRCP
MRCP is an MRI-based imaging test. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[37,38] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

U/S
Some discomforts associated with U/S include cold, unspecified pain, and tenderness. In a study comparing U/S with MRI in undiagnosed shoulder pain, 100% of the patients participating said that they would be willing to undergo the U/S exam again.[39] This test may be preferred in pediatric patients as there is no exposure to ionizing radiation, and the test does not require sedation.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

One systematic review[15] was identified that evaluated the diagnostic accuracy of cholescintigraphy with U/S in patients suspected to have acute cholecystitis. This review was somewhat dated (1994) and the majority of studies included were not head-to-head comparisons of cholescintigraphy and U/S. No systematic reviews were identified that compared cholescintigraphy with CT or MRCP. Therefore, a search for primary diagnostic accuracy studies comparing cholescintigraphy with any of the alternatives (U/S, CT, and MRCP) was conducted. Four primary studies were identifed that compared the diagnostic accuracy of cholescintigraphy to U/S.[25-28] Three of the studies reported sensitivity, specificity, or both sensitivity and specificity of the diagnostic test.[25,27,28] The other study reported only the correlation of findings between cholescintigraphy and U/S. No primary studies were found that compared cholescintigraphy with CT or MRCP.

Cholescintigraphy versus U/S

Table 3 presents the sensitivity and specificity reported in one systematic review[15] and three primary studies[25,27,28] that compared the diagnostic accuracy of cholescintigraphy and U/S for acute cholecystitis. In their systematic review, Shea et al.[15] estimated the sensitivity of cholescintigraphy and U/S to be 0.97 (95% confidence interval [CI], 0.96 to 0.98) and 0.88 (95% CI, 0.74 to 1.0), respectively. They estimated the specificity of cholescintigraphy to be 0.90 (95% CI, 0.86 to 0.95) and the specificity of U/S to be 0.80 (95% CI, 0.62 to 0.98). The sensitivity and specificity estimates incorporated an adjustment to account for verification bias.

The three primary retrospective studies all found cholescintigraphy to have higher sensitivity than U/S for the diagnosis of acute cholecystitis. Chatziioannou et al.[27] found the sensitivity of cholescintigraphy and U/S to be 0.88 and 0.50, respectively. Kalimi et al.[28] reported the sensitivity of cholescintigraphy and U/S to be 0.86 and 0.48, respectively, while Alobaidi et al.[25] reported the sensitivity of cholescintigraphy and U/S to be 0.91 and 0.62, respectively. In their study, Chatziioannou et al.[27] found the specificity of cholescintigraphy to be 0.93 compared with 0.88 for U/S. In all three of these primary studies, findings from the imaging tests were compared with histopathological findings of the same patients suspected of acute cholecystitis. In Chatziioannou et al.,[27] all 107 patients in the study underwent both cholescintigraphy and U/S.

Tables 3 and 4 present other diagnostic findings from primary studies. Chatziioannou et al.[27] found the overall accuracy of cholescintigraphy and U/S to be 0.92 and 0.77, respectively. Blaivas et al.[26] found the correlation between the diagnosis of acute cholecystitis with cholescintigraphy and U/S to be 0.74.

Table 3: Sensitivity and Specificity of Cholescintigraphy and Ultrasonography

Author	Year	Cholescintigraphy			Ultrasonography		
		N	Sensitivity (95% CI)	Specificity (95% CI)	N	Sensitivity (95% CI)	Specificity (95% CI)
Meta-analyses							
Shea et al.[15]	1994	22	0.97 (0.96 to 0.98)	0.90 (0.86 to 0.95)	5	0.88 (0.74 to 1.0)	0.80 (0.62 to 0.98)
Primary Retrospective Studies							
Chatziioannou et al.[27]	2000	107	0.88	0.93	107	0.50	0.88
Kalimi et al.[28]	2001	28	0.86 (0.67 to 0.96)	NR	50	0.48 (0.34 to 0.63)	NR
Alobaidi et al.[25]	2004	22	0.91	NR	100	0.62	NR

CI = confidence interval; N = number of patients; NR = not reported.

Table 4: Other Measures of Diagnostic Accuracy for Cholescintigraphy and Ultrasonography

Author	Year	Cholescintigraphy					Ultrasonography				
		N	PPV	NPV	Acc	Cor	N	PPV	NPV	Acc	Cor
Chatziioannou et al.[27]	2001	107	0.85	0.95	0.92	NR	107	0.64	0.80	0.77	NR
Blaivas et al.[26]	2007	102	NR	NR	NR	0.74	102	NR	NR	NR	0.74

Acc = accuracy; cor = correlation; N = number of patients; NR = not reported; NVP = negative predictive value; PPV = positive predictive value.

Cholescintigraphy versus CT
No studies were identified that compared the diagnostic accuracy of cholescintigraphy and CT scan.

Cholescintigraphy versus MRCP
No studies were identified that compared the diagnostic accuracy of cholescintigraphy and MRCP.

Details of the diagnostic accuracy studies can be found in Appendix 3.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Cholescintigraphy
Risks associated with cholescintigraphy include allergy to HIDA, pain during cholecystokinin (CCK) injection (causes gallbladder contraction), chills, nausea, and rash. In susceptible subjects, CCK has induced panic attacks.[40] Rapid administration of CCK has been associated with deterioration in blood gases and respiratory function in infants. In a study of 18 subjects, slow infusion of CCK resulted in no adverse reactions, specifically abdominal pain, which was present in the group that had a bolus injection. Slow infusion of CCK is now a well-recognized practice (MIIMAC expert opinion).

CT
Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[41] In addition, patients may experience mild side effects from the contrast agent such as nausea, vomiting, or hives. A 2009 retrospective review of all intravascular doses of low-osmolar iodinated and Gd contrast materials administered at the Mayo Clinic between 2002 and 2006 (456,930 doses) found that 0.15% of patients given CT contrast material experienced side effects, most of which were mild. A serious side effect was experienced by 0.005% of patients.[53] CT is contraindicated in patients with elevated heart rate, hypercalcemia, and impaired renal function. [42]

MRI
MRI is contraindicated in patients with metallic implants, including pacemakers.[43] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[41] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[42] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[42]

U/S
There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

Among the modalities to diagnose acute cholecystitis, cholescintigraphy, CT, and ERCP expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 5.

Table 5: Effective Radiation Doses for Various Imaging Tests

Test	Effective Radiation Dose (mSv)	Pediatric Effective Dose Estimate Range (mSv)
^{99m}Tc-disofenin	3.1[54]	NR
^{99m}Tc-mebrofenin	3.1[54]	NR
CT	8.0[44]	8.0[44]
ERCP*	1 to 10[55]	0.3 to 3[55]
MRCP (MRI)	0	0
U/S	0	0
Average background dose of radiation per year	1-3.0[44-46]	1-3.0[44-46]

CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; GI = gastrointestinal; MRCP = magnetic resonance cholangiopancreatography; NR = not reported; ^{99m}Tc-disofenin = technetium-99m disofenin; ^{99m}Tc-mebrofenin = technetium-99m mebrofenin; U/S = ultrasound.
*Based on x-ray of abdomen and upper GI series with bowel follow-through.[55]

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

Cholescintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation ofcholescintigraphy should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[56] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct hepatobiliary scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and U/S should be diagnostic radiologists[47] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[56]

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on-site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT scanners, MR scanners, and nuclear medicine equipment.[56]

CT
For the performance of CT scan, medical radiation technologists who are certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications.

MRCP
Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

U/S
Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[47] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[47]

The availability of expertise to diagnose acute cholecystitis varies across the jurisdictions. Table 6 reports the number of medical imaging professionals nationally and highlights those provinces and territories that lack a specific expertise. Gastroenterologists are not included in this list; however, the number of gastroenterologists in Canada available to perform the procedure is reported to be 1.83 per 100,000 persons.[57]

Table 6: Medical Imaging Professionals in Canada[47]

Jurisdiction	Diagnostic Radiology Physician	Nuclear Medicine Physician	Medical Radiation Technologists	Nuclear Medicine Technologists	Sonographers	Medical Physicist
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported for jurisdictions; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PEI = Prince Edward Island; QC = Quebec; YT = Yukon.
*This represents a total for all of the jurisdictions

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 7 provides an overview of the availability of equipment required to diagnose acute cholecystitis. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Data were not available for U/S.

Table 7: Diagnostic Imaging Equipment in Canada[47,48]

	Nuclear Medicine Cameras	CT Scanners	MRI Scanners	SPECT/CT Scanners
Number of devices	603[47]	460[48]	218[48]	96[48]
Average number of hours of operation per week (2006-2007)[47]	40	60	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	NU	YT, NT, NU	PE, YT, NT, NU

NT = Northwest Territories; NU = Nunavut; PE = Prince Edward Island; YT = Yukon

Cholescintigraphy
To perform cholescintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[47]

CT
No CT scanners are available in Nunavut.[48] The average weekly use of CT scanners ranged from 40 hours in PEI to 69 hours in Ontario, with a national average of 60 hours.[47] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[49]

ERCP
ERCP is an x-ray–based test. X-ray machines are widely available across the country.

MRCP
MRCP is an MRI based test. No MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[48] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario with a national average of 71 hours.[47] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[49]

U/S
U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of cholescintigraphy and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget — these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 8), the cost of cholescintigraphy with ^{99m}Tc-based radioisotopes is $298.38. CT is minimally more costly, MRCP is moderately more costly, and U/S is minimally less costly. An estimate for ERCP could not be obtained; however, actual costs (i.e., excluding professional fees) obtained from one Ontario hospital were reported to be approximately $1900. Therefore, ERCP is a significantly more costly alternative.

Table 8: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[58]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
Cholescintigraphy				
J804	First transit — without blood pool images	16.50	20.95	37.45
Y831	Biliary scintigraphy	152.69	66.24	168.40
Maintenance fees — from global budget		42.00		42.00
	TOTAL	211.19	87.19	**298.38**
CT				
X410	Abdominal CT — with IV contrast		102.65	102.65
X232	Pelvic CT — with IV contrast		102.65	102.65
Technical cost — from global budget		150.00		150.00
Maintenance fees — from global budget		28.55		28.55
	TOTAL	178.55	205.30	**383.85**
MRCP				
X451C	MRI – cannulation abdomen — multislice sequence		77.20	77.20
X455C (×3)	Repeat (another plane, different pulse sequence), to a maximum of 3 repeats		38.65 (×3) = 115.95	115.95
X499C	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.50	65.40
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		36.50		36.50
	TOTAL	336.50	258.65	**595.15**
U/S				
J135	Complete abdominal scan	50.00	34.95	84.95
Maintenance fees — from global budget		3.30		3.30
	TOTAL	53.30	34.95	**88.25**

3-D = three-dimensional; anes = anesthetic; CT = computed tomography; ERCP = endoscopic retrograde cholangiopancreatography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; RNA = radionuclide angiogram; spec = specialist; SPECT = single-photon emission computed tomography; U/S = ultrasound.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the technetium-99m (^{99m}Tc)-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to March 2, 2011>
Date of Search:	March 2, 2011
Alerts:	Monthly search updates began March 2, 2011 and ran until October 2011.
Study Types:	Health technology assessments; systematic reviews; meta-analyses; randomized controlled trials; non-randomized studies; diagnostic accuracy studies
Limits:	English language Publication years 1996-March 2, 2011 for primary studies search; no date limits for systematic review search.

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search; includes title, abstract, name of substance word, subject heading word and other text fields.
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/ri	Radionuclide imaging subheading
/du	Diagnostic use subheading

MULTI-DATABASE STRATEGY	
#	**Searches**
1	exp Cholecystitis/ or exp Cholangitis/
2	*Gallbladder Diseases/ri or *Gallbladder/ri
3	Cholecystitis.ti,ab.
4	((Gallbladder* or Gall Bladder*) adj3 (inflammation or Empyema)).ti,ab.
5	or/1-4
6	Technetium/
7	exp Technetium Compounds/
8	exp Organotechnetium Compounds/
9	exp Radiopharmaceuticals/

MULTI-DATABASE STRATEGY	
10	(Technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc* or 99mtechnetium* or 99m-technetium*).tw,nm.
11	Radionuclide Imaging/ or Perfusion Imaging/
12	radionuclide imaging.fs.
13	radioisotope*.mp.
14	((radionucl* or nuclear or radiotracer* or hepatobiliary or hepato-biliary or sulfur colloid* or gall bladder* or gallbladder*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
15	Tomography, Emission-Computed, Single-Photon/
16	(single-photon adj2 emission*).ti,ab.
17	(SPECT or scintigraph* or scintigram* or scintiphotograph* or Cholescintigraph*).ti,ab.
18	(lidofenin or gadolinium-HIDA or Gd-HIDA or iminodiacetic acid or HIDA or 99mTc-IDA).tw,nm.
19	(59160-29-1 or 73121-98-9).rn.
20	or/6-19
21	meta-analysis.pt.
22	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
23	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
24	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
25	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
26	(data synthes* or data extraction* or data abstraction*).ti,ab.
27	(handsearch* or hand search*).ti,ab.
28	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
29	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
30	(meta regression* or metaregression* or mega regression*).ti,ab.
31	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
32	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
33	(cochrane or health technology assessment or evidence report).jw.
34	or/21-33
35	5 and 20 and 34
36	exp "Sensitivity and Specificity"/
37	False Positive Reactions/
38	False Negative Reactions/
39	du.fs.
40	sensitivit*.tw.
41	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti,ab.
42	(predictive adj4 value*).tw.
43	Comparative Study.pt.
44	(Validation Studies or Evaluation Studies).pt.
45	Randomized Controlled Trial.pt.
46	Controlled Clinical Trial.pt.

MULTI-DATABASE STRATEGY	
47	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
48	Multicenter Study.pt.
49	(random* or sham or placebo*).ti.
50	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
51	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
52	(control* adj3 (study or studies or trial*)).ti.
53	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
54	(allocated adj "to").ti,ab.
55	Cohort Studies/
56	Longitudinal Studies/
57	Prospective Studies/
58	Follow-Up Studies/
59	Retrospective Studies/
60	Case-Control Studies/
61	Cross-Sectional Study/
62	(observational adj3 (study or studies or design or analysis or analyses)).ti.
63	cohort.ti.
64	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
65	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
66	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
67	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
68	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
69	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
70	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
71	(population adj3 (study or studies or analysis or analyses)).ti.
72	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
73	or/37-72
74	5 and 20 and 73
75	74 not case reports.pt.
76	76
77	limit 77 to english language
78	77
79	limit 78 to yr="1996 -Current"

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library (Issue 2, 2011)	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 3 to 4, 2011
Keywords:	Included terms for cholecystitis and radionuclide imaging
Limits:	English language

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Diagnostic Accuracy Studies

Shea et al.[15]
Shea et al.[15] conducted a systematic review and meta-analysis in order to estimate the diagnostic accuracy of various tests for biliary tract disease. Acute cholecystitis was one of the biliary diseases that were evaluated. The authors searched for studies published from 1966 to September 1992 on MEDLINE. Bibliographies of selected studies were also reviewed for relevant articles. The search identified articles with MeSH descriptors or either cholelithiasis or cholecystitis AND MeSH descriptors of any of cholecystography, ultrasonography, ultrasonics, tomography, nuclear magnetic resonance, or radionuclide imaging.

Titles and abstracts of potential articles were screened by research staff. The full text of articles included after title and abstract screening was screened for inclusion by research staff and by a review committee if the research staff could not determine whether it should be included. Article exclusion criteria included the absence of original study data, sample size less than 20, inability to calculate sensitivity and specificity from data presented, atypical patient population, retrospective review, lack of description of criteria for positive diagnosis, whether the study used an atypical or outdated variant of a diagnostic test, the diagnosis was not confirmed with an acceptable gold standard, or more than 10% of patients were unavailable for follow-up.

Sensitivity and specificity for the tests were pooled by what the authors describe as cluster sampling methods for estimating a proportion. The authors corrected their estimate to account for verification bias. The authors state that most diagnostic test studies suffer from verification bias because only a subset of patients have their diagnosis verified with a gold standard. In the case of patients with gallstones, more patients with a positive imaging test result are likely to have the most common gold standard, cholecystectomy.

Twenty articles, with a total of 2,466 patients, were included in the cholescintigraphy diagnostic accuracy estimates. Five studies, with a total of 532 patients, were used to estimate diagnostic accuracy of ultrasound (U/S). The authors estimated sensitivity and specificity of cholescintigraphy to be 0.97 (confidence interval [CI], 0.96 to 0.99) and 0.90 (0.86 to 0.95), respectively. No verification bias adjustment was made for cholescintigraphy.

The authors estimated verification bias adjusted sensitivity and specificity of U/S to be 0.88 (0.74 to 1.00) and 0.80 (0.62 to 0.98), respectively. The unadjusted sensitivity and specificity of U/S was estimated to be 0.94 (0.92 to 0.96) and 0.78 (0.61 to 0.96), respectively.

Chatziioannou et al.[27]
Chatziioannou et al.[27] compared the diagnostic accuracy of cholescintigraphy and U/S for the diagnosis of acute cholecystitis. One hundred and seven consecutive patients presenting to a United States hospital emergency department during 1996 suspected of acute cholecystitis were included in the study. Patients received both cholescintigraphy and U/S at the time of presentation. For patients who went on to surgery (n = 44), pathological findings were used as the gold standard with which imaging findings were compared. For patients who did not go on to surgery (n = 63), the diagnosis made by the primary physician was considered to be the gold standard with which results from imaging tests were compared. For cholescintigraphy, nonvisualization of the gallbladder either three to four hours after radiotracer injection or 30 minutes after radiotracer and morphine sulfate injection was considered consistent with acute cholecystitis. The primary finding from U/S that was considered consistent with acute cholecystitis was sonographic Murphy's sign. In the absence of Murphy's sign, other findings considered consistent with acute cholecystitis were gallstones and gallbladder wall thickness

greater than 4 mm, gallstones, and a gallbladder more than 5 cm in length. Acalculous acute cholecystitis was diagnosed with findings of thickened gallbladder wall, edema within the wall, sludge pericholecystic fluid, and sonographic Murphy's sign.

The authors presented results separately for all patients, and for patients who went on to surgery and had pathologic confirmation of presence or absence of acute cholecystitis. For all patients, the sensitivity, specificity, positive predictive value, negative predictive and overall accuracy of cholescintigraphy was estimated to be 0.88, 0.93, 0.85, 0.95, and 0.92. For U/S, the sensitivity, specificity, positive predictive value, negative predictive and overall accuracy was estimated to be 0.50, 0.88, 0.64, 0.80, and 0.77.

For the 44 patients who went on to surgery, the sensitivity, specificity, positive predictive value, negative predictive and overall accuracy of cholescintigraphy was estimated to be 0.92, 0.89, 0.92, 0.89, and 0.91. For U/S, the sensitivity, specificity, positive predictive value, negative predictive and overall accuracy was estimated to be 0.40, 0.89, 0.83, 0.53, and 0.61.

Alobaidi et al.[25]
Alobaidi et al.[25] reviewed data from 117 patients pathologically proven to have acute cholecystitis. Patients were seen in a United States hospital between 1999 and 2002. Patients were stratified into groups depending on which imaging test (U/S, cholescintigraphy) or combination of imaging tests they underwent before surgery. The diagnoses made with each test at the time of exam were used to calculate each test. False-negative U/Ss were reviewed by radiologists, along with 40 true-positive scans from the same group as a control. The review was used to estimate a corrected sensitivity estimate to account for what the authors refer to as limiting factors relating to the date of surgery versus the date of imaging. Criteria used to diagnose acute cholecystitis with U/S included sonographic Murphy's sign, gallbladder wall thickening, pericholecystic fluid, biliary dilatation, and gallbladder hydrops. Diagnosis of acute cholecystitis with cholescintigraphy was based on nonvisualization of the gallbladder three hours after injection of radiotracer or 30 minutes after injection of morphine sulfate. Ninety-seven of the 117 patients had U/S as their initial imaging test. Based on initial diagnosis, the authors reported sensitivity for U/S of 62%. Nine false-negative patients reclassified as true positives upon additional review by radiologists. Based on this reclassification, the sensitivity of U/S was estimated to be 70.4%. The authors estimated the sensitivity of cholescintigraphy to be 90.9%.

Kalimi et al.[28]
Kalimi et al.[28] retrospectively reviewed 132 patients admitted to a United States hospital emergency room with upper quadrant pain between 1996 and 2000. These patients were pathologically proven to have acute cholecystitis. At the time of presentation at the emergency room, patients were tested either by means of cholescintigraphy (n = 28), U/S (n = 28), or both cholescintigraphy and U/S (n = 54). Sensitivity for each test or combination of tests was estimated by the number of positive findings at the time of admission. Cholescintigraphy was considered to be positive for acute cholecystitis if there was nonvisualization of the gallbladder despite morphine augmentation. U/S findings considered positive for acute cholecystitis was presence of gallstones along with either wall edema or stone impacted in the gallbladder neck. The authors report the sensitivity of cholescintigraphy and U/S to be 86% (95% CI, 67% to 96%) and 48% (95% CI, 34% to 63%), respectively. The sensitivity for patients undergoing both cholescintigraphy and U/S was 90% (95% CI, 80% to 97%).

Blaivas et al.[26]

Blaivas et al.[26] retrospectively compared findings from U/S and cholescintigraphy in patients suspected of acute cholecystitis. A total of 99 patients presenting at a United States hospital emergency department who received both U/S and cholescintigraphy were included in the study. U/S findings that were considered to be indicative of acute cholecystitis included finding of gallstones with a sonographic Murphy's sign, significant wall thickening greater than 5 mm, pericholecystic fluids, or a combination of these. No gold standard was specified in the study and no estimates of sensitivity or specificity were reported. The authors did report an overall correlation of findings between cholescintigraphy and U/S of 0.74. The authors also reported that U/S diagnosed acute cholecystitis in 38% of the 38 patients diagnosed with cholescintigraphy. Of the 25 patients diagnosed with acute cholecystitis using U/S, 80% were diagnosed positive using cholescintigraphy.

APPENDIX 2.13

INDICATION OVERVIEW

Kidney transplantation is a treatment option for end-stage renal disease (ESRD). It can help to restore patients' quality of life and reduces morbidity and mortality rates in patients with renal failure.[1] However, several complications can occur after transplantation and may result in impaired renal function. These complications can be classified as surgical or medical. Immediate surgical complications include renal artery thrombosis or stenosis, renal vein thrombosis, or urinary leak. Medical complications include organ/tissue rejection, drug toxicity related to anti-rejection treatments (e.g., cyclosporine), acute tubular necrosis (ATN), infection, and transplantation-related malignancies (e.g., post-transplantation lymphoproliferative disorder or lymphoma).[2-4] Obstruction in a renal transplant can also occur and result in paranchymal damage due to increased pressure in the collecting system.[5]

The most common complication of kidney transplantation is allograft dysfunction (dysfunction of the transplanted kidney). This can take place as early as in the operating room (considered "very early" dysfunction), as an early dysfunction (one to 12 weeks post-transplant), or as a late dysfunction (later than three months).[6] Symptoms include an acute rise in serum creatinine, decreased urine production, increased blood pressure, pyuria (white blood cells in urine), and proteinuria (protein in the urine). The focus of this report is on acute rejection.

Acute rejection, ATN, and cyclosporine toxicity are the most common causes of early transplant failure.[4,7,8] These complications may result in deterioration of renal function as a late permanent event. Therefore, careful monitoring of patients following a kidney transplant is required to detect complications before severe damage occurs.[1,9] The common methods of monitoring include the clinical assessment of the patient, ultrasound (U/S) examinations (grey scale and Doppler), isotope-based studies (e.g., renal scintigraphy), needle core biopsy, and fine-needle aspiration biopsy with cytology.[1,8,9]

Population: Patients who received kidney transplants being evaluated for acute rejection.

Intervention: Renal scintigraphy (also referred to as renal scan) using technetium-99m(^{99m}Tc)–labelled radiopharmaceuticals.

Renal scintigraphy has been used to assess the structure, blood flow, and function of kidney transplants.[3,5] With nuclear imaging, the radiolabelled isotopes permit the mapping of blood flow through the kidney. This allows the imaging of blood flow, obstructions, or leaks in the newly transplanted kidney.[10]

During renal scintigraphy, a radiopharmaceutical is administered, and gamma rays emitted from the patient are externally detected with a gamma camera to produce images that reflect the distribution of the radioactive agent.[11] Two ^{99m}Tc-labelled radiopharmaceuticals that have been used for dynamic renal scintigraphy include ^{99m}Tc-diethylenetriamine pentaacetic acid (DTPA) and ^{99m}Tc-mercaptoacetyl triglycine (MAG3).[12] ^{99m}Tc-DTPA does not defuse into cells due to its lipid insolubility, and is almost entirely removed from circulation by glomerular filtration. Early images with this agent provide information about renal perfusion, whereas delayed images provide information about glomerular filtration rate (GFR), indicating changes in renal function.[12]

^{99m}Tc-MAG3 is rapidly taken by the kidneys and excreted into the urinary tract.[11] Because of the higher extraction efficiency, ^{99m}Tc-MAG3 may be preferred over ^{99m}Tc-DTPA, especially in patients with decreased renal function.[12,13] Using renal scintigraphy, graft function can be assessed both qualitatively and quantitatively.[14]

The quantitative evaluation of the graft (i.e., transplanted kidney) function is based on the time-activity curves, known as renograms, which reflect three sequential phases of renal function:[5,15,16]

- Vascular phase, or flow study, shows the transit of radiotracer through the blood vessels (performed within approximately five seconds after administration of the radiopharmaceutical)
- Parenchymal or function phase is the period in which the nephrons extract the tracer from the blood and excrete it by glomerular filtration or tubular secretion (performed two to three minutes after administration of the radiopharmaceutical)
- Washout or excretory phase is the period during which the tracer drains through the renal pelvis to the bladder (performed 20 to 30 minutes after administration of the radiopharmaceutical in a normally hydrated patient).

A renogram of a normal kidney shows rapid increase during the vascular and parenchymal phases, followed by rapid decline during the excretory phase.[11]

Various quantitative indices have been proposed to evaluate the handling of the tracer by the kidney. The two widely used indices in vascular phase, Hilson's perfusion index and Kirchner's kidney/aorta ratio, reflect the relationship between renal blood flow in the graft and the blood flow in the iliac artery or abdominal aorta. These indices allow the differential diagnosis between ATN and acute rejection. Blood flow of the transplanted kidney is less affected in patients with ATN than in patients with acute rejection.[5] To evaluate the function of transplanted kidney, two types of quantitative measures are used: indices of renal function (e.g., tracer uptake capacity, GFR, effective renal plasma flow [ERPF], clearance index) and indices of tracer transit (e.g., mean transit time, excretory index).[5] Decreased uptake in the parenchymal phase and prolonged washout in the excretory phase are quantitative scintigraphic features of ATN and acute rejection.[11] Accumulation of radiotracer activity in the collecting system is often observed in patients with obstruction.[5]

Comparators: For this report, the following diagnostic test is considered as an alternative to renal scintigraphy:

- U/S is commonly performed in renal transplant patients, from the immediate post-operative period to long-term follow-up.[7,8] This modality can also be used to guide other more invasive diagnostic tests. For example, it is used to guide the needle in renal biopsy so that a desired tissue can be removed with less damage and complications.[14] In U/S, both the internal renal morphology (e.g., renal enlargement, heterogeneity of renal cortex, hypoechogenicity of renal pyramids and cortex, thickening of the walls of the renal collecting system) and the perinephric complications of kidney transplant, such as perinephric fluid collection, can be examined.[4,14] Doppler U/S is used for detection of vascular complications.[4,8] The two most commonly used quantitative Doppler indices include resistive index and pulsatility index.[1,4] Other measures such as systolic-to-diastolic and diastolic-to-systolic ratios have also been used to show the Doppler spectrum.[1] More advanced U/S techniques, including duplex U/S and colour Doppler, may be used to diagnose vascular complications in a transplanted

kidney.[4] Sequential ultrasonographic studies may be required in the early post-operative period.[1]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library (2011, Issue 2) via Wiley; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and kidney transplantation.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. The search was limited to English language documents. No date or human limits were applied for the systematic reviews search. For primary studies, the retrieval was limited to the human population and to documents published between January 1, 1996 and March 14, 2011. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

There were five potential clinical articles identified through the meta-analyses/systematic review/health technology assessment (MA/SR/HTA) filtered search, none of which were relevant. A total of 404 potential primary studies were identified with the primary studies search and 47 articles underwent full-text review. No randomized controlled trials (RCTs) reporting on the accuracy of diagnostic tests of interest, patients outcomes, or quality of life were found. Seven observational studies reported on the relative diagnostic accuracy of renal scintigraphy and the alternative tests of interest.[17-23]

The original search did not capture studies evaluating the diagnostic accuracy of fine-needle aspiration biopsy (FNAB) compared to renal scintigraphy or vice versa. One older study comparing FNAB, renal scintigraphy, and U/S to core needle biopsy was found from the reference lists of the included articles.[24] The remaining articles from the database searches, along with other articles found through searching the grey literature, articles from the targeted searches, or articles from the reference lists of the identified potential articles, were used to abstract information relevant to the remaining criteria.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	The potential population requiring post-transplant renal scintigraphy or its alternatives includes all patients who have received kidney transplants. The prevalence rate of patients living with kidney transplants was 4.57 per 10,000 population in 2009.[25] It is assumed that fewer than 20% of these patients require imaging in a given year. The size of the affected population is less than 1 in 10,000 (0.01%).
2	**Timeliness and urgency of test results in planning patient management**	According to the urgency classifications developed by the province of Saskatchewan, it is recommended that renal scintigraphy be performed within the first 24 hours after transplantation in cases of suspected acute rejection (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). Early diagnosis and careful management of complications prevents premature loss of the kidney transplant and reduces patient mortality and morbidity.[1,4,26,27] The target time frame for performing the test is in 24 hours or less, and obtaining the test results in the appropriate timely manner for the underlying condition has moderate to significant impact on the management of the condition or the effective use of heath care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	No studies evaluating the effect of diagnostic modalities as factors influencing patient survival after kidney transplants were identified. However, two studies[28,29] reported that renal transplant complications can significantly reduce graft and patient survival rates. Based on the risks associated with renal transplant complications, early recognition and intervention are important. Diagnostic imaging test results are assumed to have a minimal impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Two studies[28,29] reported that renal transplant complications can significantly reduce graft and patient survival rates. Patients with graft failure may resume dialysis or be listed for repeat transplantation.[28] They also may experience a higher number of rejection episodes per year, a higher number of hospitalizations, and longer hospital stays.[30] Patients who return to dialysis after transplant failure may show poorer quality of life.[31] Graft failure may be followed by grief and denial, and may trigger a depressive state.[31] Based on the risks associated with renal transplant complications, early recognition and interventions are important. Diagnostic imaging results are assumed to have a significant impact on morbidity and quality of life.

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>5</td><td>Relative impact on health disparities</td><td>To be scored locally.</td></tr>
<tr><td>6</td><td>Relative acceptability of the test to patients</td><td>Renal scan is reported to be well-tolerated.[12] Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Bladder catheterization may be required and catheterization may be associated with some discomfort, particularly in pediatric patients.[32]

Some discomforts associated with U/S include cold, unspecified pain, and tenderness. This test may be preferred in pediatric patients, as there is no exposure to ionizing radiation and U/S does not require sedation.

Renal scan using ^{99m}Tc-radiolabelled isotopes:
• is minimally less acceptable than U/S.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>Four observational studies[17,18,24,33] on the relative diagnostic accuracy of renal scintigraphy, U/S, and biopsy were included in this review. Biopsy was used as the gold standard in the majority of the included studies.

<table>
<tr><th>Study (year)</th><th colspan="2">Renal Scan</th><th colspan="2">U/S</th></tr>
<tr><th></th><th>Sensitivity (%)</th><th>Specificity (%)</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>Kim et al. (2005)[33]</td><td>N/A</td><td>N/A</td><td>85</td><td>90</td></tr>
<tr><td>Isiklar et al. (1999)[18]</td><td>59</td><td>57</td><td>81</td><td>57</td></tr>
<tr><td>Aktas et al. (1998)[17]</td><td>45 to100</td><td>N/A</td><td>36 to 88</td><td>N/A</td></tr>
<tr><td>Delaney, et al. (1993)[24]</td><td>70</td><td>N/A</td><td>43</td><td>N/A</td></tr>
</table>
N/A = not available; U/S = ultrasound.</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		Based on the available evidence, the diagnostic accuracy of renal scanning using ^{99m}Tc-radiolabelled isotopes is: • similar to that of U/S.
8	**Relative risks associated with the test**	Adverse events from renal scintigraphy are rare but may include reaction to the radiopharmaceutical, rash, fever, or chills.[34] Patients are exposed to ionizing radiation. There are no reported risks associated with U/S in the literature that was reviewed. Overall, renal scanning using ^{99m}Tc-radiolabelled isotopes is: • minimally less safe than U/S.
9	**Relative availability of personnel with expertise and experience required for the test**	As of 2006 in Canada, there were 2,034 diagnostic radiologists, 221 nuclear medicine physicians, 12,255 radiological technologists, 1,781 nuclear medicine technologists, and 2,900 sonographers available across Canada. YT, NT, and NU do not have the available personnel to perform and interpret tests to evaluate renal function in transplant patients. Other jurisdictions (e.g.,PEI) may offer limited nuclear medicine services. Assuming the necessary equipment is available, if ^{99m}Tc imaging using renal scanning is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using U/S.
10	**Accessibility of alternative tests (equipment and wait times)**	For renal scans, nuclear medicine facilities with gamma cameras (including SPECT) are required. No nuclear medicine cameras are available in the YT, NT, or NU.[35] In 2007, the latest year for which data are available, the average wait time for renal scintigraphy at MUHC hospitals was 13 days. However, the wait times were reported to be less than one day for emergency cases.[36] In 2009, there were 23 active kidney transplant programs in Canada, operating in seven provinces (AB, BC, MB, NS, ON, QC, and SK).[25] No information was found on the accessibility of U/S in Canada. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[37] Ontario had the shortest wait time (two weeks), whereas patients in Quebec experienced the longest wait time (eight weeks) for U/S.[37] Assuming the necessary expertise is available, if ^{99m}Tc imaging using renal scanning is not available, it is estimated that:

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>• more than 95% of the procedures can be performed in a timely manner using U/S.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of renal scintigraphy with ^{99m}Tc-based radioisotopes is $241.95. U/S is a minimally less costly alternative.
<table>
<tr><th colspan="3">Relative Costs</th></tr>
<tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr>
<tr><td>Renal scintigraphy</td><td>241.95</td><td>Reference</td></tr>
<tr><td>U/S</td><td>44.60</td><td>–197.35</td></tr>
</table></td></tr>
</table>

AB = Alberta; BC = British Columbia; MB = Manitoba; MUHC = McGill University Health Centre; N/A = not available; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; ON = Ontario; PEI = Prince Edward Island; QC = Quebec; SK = Saskatchewan; SPECT = single-photon emission tomography; ^{99m}Tc = technetium-99m; U/S = ultrasound; YT = Yukon.

CRITERION 1: Size of affected population (link to definition)

The potential population requiring post-transplant renal scintigraphy or its alternatives includes patients who have received kidney transplants. This includes newly transplanted kidneys (incident cases), as well as the total number of patients living with functioning transplanted kidneys (prevalent cases). According to the Canadian Organ Replacement Register (CORR), a registry of the Canadian Institute for Health Information,[25] 1,171 Canadians adults and 53 children received kidney transplants in 2009. As of December 31, 2009, the prevalence of people living with a functioning kidney transplant in Canada was 15,434 (4.57 per 10,000).[25] Of 10,641 kidney transplant procedures registered with CORR between 2000 and 2009, 1,141 (11%) were retransplants.[25] It is assumed that only a proportion of these patients require imaging in a given year.

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Early diagnosis and careful management of complications prevents premature loss of the kidney transplant and reduces patient mortality and morbidity.[1,4,26,27] Timely diagnosis is particularly important in young children: renal graft outcomes can be less favourable than in older recipients, due to more intense immune-reactivity and higher graft rejection rates in children, as well as inconsistent adherence to medication in this group of transplant recipients.[27] Baseline imaging studies should be performed immediately after transplantation, as the diagnosis of complications can be made based on changes in the results of imaging studies over time.[4]

According to the Saskatchewan hospital guidelines, renal scintigraphy should be performed within the first 24 hours after transplantation in cases of suspected acute rejection (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). The suggested renal scintigraphy wait time targets for patients with suspected renal artery stenosis, urinary leak, or obstructive uropathy after transplantation is two to seven days (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). The same guidelines indicate that U/S for diagnosis of renal transplant rejection should be conducted within two to seven days after transplantation (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). However, the use of U/S is suggested within the first 24 hours in cases with suspected thrombosis of renal artery or vein (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011).

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Kidney transplant patients are at risk of complications, including loss of transplant function. Timely diagnosis of these complications is important in order to reduce patient mortality and morbidity.[4] Some cases of acute rejection and ATN may not present clinical symptoms.[1] Failure to perform the appropriate imaging tests may result in increased rates of graft dysfunction (due to delayed or inappropriate treatment) and post-transplant mortality.

Two studies evaluating the relationship between kidney graft function and patient survival were identified through targeted searches.[28,29]

In 2005, Knoll et al. published a retrospective cohort study on the effects of functional renal transplant loss on patient survival, using the data from the CORR (n = 4,743 primary renal transplant recipients transplanted between 1994 and 1999).[28] In five years of follow-up, 411 patients (8.7%) died.[28] One-hundred and three deaths were attributed to graft failure.[28] The unadjusted death rate was 5.14 per 100 patients with kidney transplant failure.[28] After controlling for possible confounding variables (e.g., recipient age, gender, race, cause of ESRD, comorbidity, pretransplant dialysis time, donor source, and donor age), transplant failure was shown to significantly increase the risk of death more than three times, as compared with patients who maintained transplant function (adjusted hazard ratio = 3.39; 95% Confidence Interval [CI], 2.75 to 4.16; P < 0.0001).[28] The authors concluded that kidney transplant failure following renal transplantation is a significant predictor of mortality.[28]

A previous study (1999) by Woo et al. investigated the association between graft and patient survival rates (n = 589 patients who received their first kidney transplants from deceased donors between 1984 and 1993).[29] The median follow-up time was seven years.[29] Patient survival rates were 95%, 82%, and 65% at one, five, and 10 years after transplantation, respectively.[29] One-hundred and sixty-eight patients (28.5%) died during follow-up; 79 (47% of all deaths) were due to transplant failure. In this study, good graft function (serum creatinine levels < 200 µmol/L) at three months was associated with significantly improved long-term graft survival (P < 0.001). Long-term survival was higher for patients with functioning grafts (85% and 70% at five and 10 years, respectively) than for those who had graft failure (75% and 56%, at five and 10 years, respectively; P = 0.004 for log-rank test). The authors concluded that patient survival after kidney transplant is related to graft outcomes, and that patients with early graft rejection, or early graft loss, are at increased risk of mortality.

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

One of the main goals of kidney transplantation is to improve patient quality of life.[38]
Two studies evaluating the relationship between kidney graft function and patient morbidity or quality of life were identified through targeted searches.[30,31]

In 2006, Ouellette et al.[31] performed a qualitative literature review on the psychological impacts of renal graft loss. The following findings of the reviewed studies were discussed in the article:

- Patients who return to dialysis after graft failure show a poorer health-related quality of life (HQoL) than dialysis patients who have never received a renal transplant.

- Reaction to graft failure and its impact on quality of life may vary from patient to patient.
- Patients may react to graft loss in two different ways: grief and denial.
- The grieving process may include feelings of guilt, depression, irritability, anger, or sadness, as well as concerns about the impact of graft loss on patient's future lifestyle.
- Patients who go through the denial process after graft loss do not show any emotional response to graft failure.
- People who experience graft failure may also report feelings of loss of control over their life, guilt about the donated kidney being wasted, and failure in fulfilling others' expectations.

A 1999 study by Aultman et al.[30] followed 179 consecutive renal transplant recipients grouped according to their length of graft success: failure within six months of implantation (n = 18), failure between six months and three years (n = 41), and grafts surviving longer than three years (n = 120). As would be expected, those transplant recipients with grafts surviving longer than three years experienced the greatest benefit.[30] Patients with primarily successful renal transplants (grafts surviving longer than six months, but less than three years) experienced a significantly greater number of complications and more serious, life-threatening outcomes (i.e., bacterial sepsis, pneumonia, severe wound infection) when compared with either of the two other groups (see Table 2).[30]

Table 2: Morbidity Associated With Graft Rejection[30]

	Group 1: Graft Failure Within Six Months of Implantation (n = 18)	**Group 2: Graft Failure Between Six Months and Three Years (n = 41)**	**Group 3: Grafts Surviving Longer Than Three Years (n = 120)**	**P**
Rejections per patient/year	0.6	2.4	0.5	< 0.0001
Hospitalizations per year	1.3	3.0	0.8	< 0.0001
Days in hospital per year	20	31	6	< 0.0001
Complications per patient	1.1	1.3	0.6	< 0.0001
Patient survival (%)	83	76	90	

If a test was not available to monitor the transplanted kidney, patients would risk more severe and permanent complications — such as graft lost, for example. Patients with known graft failure may resume dialysis, or be listed for repeat transplantation.[28]

Return to Summary Table.

CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

Health disparity might be present if disadvantaged social groups systematically experience worse health or more health risks than do more advantaged social groups.[39] Disadvantaged groups can be defined based on gender, age, ethnicity, geography, disability, sexual orientation,

socioeconomic status, and special health care needs. Our targeted search found disparity concerns in the following disadvantage groups:

Racial and ethnic groups

Matsuda-Abedini et al.(2009)[40] conducted a retrospective, single Canadian centre database review to determine the short- and long-term outcomes of kidney transplantation in Aboriginal children compared to non-Aboriginals in British Colombia. Of the 159 kidney transplant recipients included in this study, 15% were Aboriginal.[40] At the end of first year post-transplant, there was no difference between Aboriginal and non-Aboriginal children regarding early transplant outcomes such as delayed graft function, episodes of acute rejection, and estimated glomerular function rate.[40] However, Aboriginal kidney recipients had a significantly lower long-term transplant survival than the non-Aboriginal group (delayed rejection rate: 50% versus 26.7%, P = 0.03).[40] Assuming uniform access to health care across the province of British Columbia, the authors attributed the difference in outcomes observed in Aboriginal and non-Aboriginal children to a combination of factors:

- the different etiology of ESRD (glomerulonephritis is the most common cause of ESRD among Aboriginals versus congenital abnormalities of the urinary tract among non-Aboriginals)
- the different rates of pre-emptive transplants (none of the Aboriginal patients received a preventative transplantation versus 22% of non-Aboriginals transplant recipients who had not been exposed to dialysis).[40]

Health care centre variations

Kim et al.(2004)[41] studied 5,082 Canadian patients who received kidney transplantation between 1988 to 1997, across 20 transplant centres. Patients were followed from the date of transplantation to the time of graft failure, death, or end of study (December 31, 1997).[41] Centre-specific, covariate-adjusted hazard ratios were calculated.[41] These can be interpreted as the covariate-adjusted rate for a given centre, divided by the covariate-adjusted rate for all remaining centres.[41] Graft failure (including patient death) hazard ratios varied from 0.51 (approximately 49% lower graft failure, relative to the remaining centres) to 1.77 (approximately 77% higher graft failure rates, relative to the remaining centres).[41] Covariate-adjusted hazard ratios for mortality varied from 0.44 to 1.84.[41] Six centres showed significantly elevated rates of graft loss (range: 1.36 to 1.84; i.e., 36% to 84% higher than other centres), whereas five centres showed significantly decreased rates (range: 0.44 to 0.65; i.e., 35% to 66% lower than other centres).[41] Patient death and graft loss rates were lower in larger centres (with ≥ 200 transplants over the study period).[41] The variation in transplant outcomes persisted after adjustment for known prognostic factors such as recipient age, proportion of deceased- and living-donor transplants performed, and the percentage of patients with diabetes.[41] In addition, disparities in centre-specific outcomes increased with increasing time from transplantation (at one, three, and five years).[41] The authors concluded that significant centre-specific variation in the success of renal transplantation exists in Canada.[41] This disparity could be impacted by a lack of availability to imaging, particularly if smaller centres have more difficulties acquiring ^{99m}Tc-based radiopharmaceuticals and accessing alternate imaging modalities.

Gender

Liu et al. (2007)[42] evaluated the effect of gender on HQoL in 66 female and 72 male kidney transplant recipients in one American transplant centre. HQoL was measured using the SF-36 Health Survey.[42] Women reported significantly lower scores on the SF-36 physical functioning (P = 0.049), role-physical (P = 0.014), and bodily pain (P = 0.028) scales.[42] The authors concluded that women may experience worse physical functioning and more body pain and face

more problems with work and other daily activities than men.[42] They suggested that the study findings could be used in developing interventions to optimize HQoL in renal transplant patients.[42]

Level of education
Schaeffner et al.(2008)[43] investigated the relationship between level of education and transplantation outcomes in 670 American patients who received renal transplants between 1996 and 1997.[43] There was no significant association between educational level and graft failure.[43] However, the rates of graft loss from causes other than death significantly decreased from lowest to highest level of education, so that patients who had a college degree had 43% lower rates of graft loss than the ones who did not complete high school (relative risk: 0.57, 95% CI, 0.31 to 1.04; P-value for trend = 0.03).[43] The authors suggested that the greater risk of graft loss in patients with lower education might be related to comorbidities and poor medication adherence.[43]

Socioeconomic status
In a single-centre study in the United Kingdom, Stephens et al. (2010) investigated the impact of socioeconomic deprivation on post-transplant outcomes in 621 renal transplant recipients.[44] Patients in the most income-deprived group had a significantly higher rate of acute rejection than the ones in the least income-deprived group (36% versus 27%, P = 0.013).[44] Income deprivation was significantly associated with five-year graft survival (log-rank test for least deprived versus most deprived, P = 0.018).[44] The authors concluded that socioeconomic deprivation might adversely influence outcomes following renal transplantation.[44]

Return to Summary Table.

CRITERION 6: Relative acceptability of the test to patients (link to definition)

Renal scintigraphy
Overall, renal scan is reported to be well-tolerated.[12] However, patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Intravenous fluids might be required if the adequacy of hydration is a concern.[45] Because a full bladder may slow drainage of the radiopharmaceutical from the upper part of the urinary tract, the bladder should be emptied frequently. Bladder catheterization may be required, especially in pediatric patients. Catheterization may be associated with some discomfort, particularly in children.[32]

U/S
Some discomforts associated with U/S include cold, unspecified pain, and tenderness. This test may be preferred in pediatric patients, as there is no exposure to ionizing radiation, and the test does not require sedation.

Return to Summary Table.

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Four observational studies[17,18,24,33] on the relative diagnostic accuracy of renal scintigraphy and U/S were included in this report. The studies focus primarily on the diagnostic accuracy of ^{99m}Tc-labelled radiotracer scintigraphy compared with renal biopsy. One study directly compared U/S to renal scintigraphy.[33] One older study comparing FNAB, renal scintigraphy, and U/S to core needle biopsy was found from the reference lists of the included articles.[24] Detailed

descriptions of the individual studies can be found in Appendix 4. The methods and results of the included studies are summarized in tabular form in Appendix 5.

Table 3: Relative Diagnostic Accuracy of Renal Scan and U/S

Study (year)	Population (n)	Outcome	Standard of Reference	Renal Scan		U/S	
				Sens. (%)	Spec. (%)	Sens. (%)	Spec. (%)
Kim et al. (2005)[33]	Adults (100)	Evaluation of renal perfusion	Renal scan	N/A	N/A	85	90
Isiklar et al. (1999)[18]	Adults (29)	Acute renal transplant rejection	Renal biopsy	59	57	81	57
Aktas et al. (1998)[17]	Patients with biopsy-proven acute rejection (26)	Acute renal transplant rejection	Renal biopsy	45 to 100	N/A	36 to 88	N/A
Delaney et al. 1993)[24]	Adults (150); episodes of allograft dysfunction, 128 transplant recipients)	Acute renal transplant rejection	Core needle biopsy	70	N/A	43	N/A

ATN = acute tubular necrosis; N/A = not available; Sens. = sensitivity; Spec = specificity; U/S = ultrasound.

Renal scintigraphy versus U/S

One study[33] compared the diagnostic accuracy of harmonic U/S (with microtubular contrast agent) to renal scintigraphy in the diagnosis of renal perfusion abnormalities.[33] In this study, the sensitivity and specificity of harmonic U/S was reported to be 85% and 90%, respectively.[33]

Two studies[17,18] compared the diagnostic accuracies of renal scintigraphy and U/S, using renal biopsy as the gold standard. Isiklar et al. (1999) found power Doppler U/S to be more sensitive than renal scintigraphy (81% versus 59%) in detecting post-transplant renal perfusion impairments.[18] A year earlier, Aktas et al. (1998) reported the overall sensitivity of renal scintigraphy to be higher than that of both gray scale and Doppler U/S.[17]

Renal scintigraphy, Doppler U/S, and FNAB versus biopsy

Delaney et al.(1993)[24] compared renal scintigraphy, Doppler U/S, and FNAB, using biopsy as the gold standard. Scintigraphy was found to be the most sensitive method for detection of acute rejection (70%) during the early post-transplant period, FNAB had a sensitivity of 52%, and U/S a sensitivity of 43%.

Return to Summary Table.

CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Renal scan
Adverse events from renal scintigraphy are rare but may include reaction to the radiopharmaceutical, rash, fever, or chills.[34] There is also a relative contraindication in the administration of captopril in patients with a solitary kidney, as it may precipitate transient acute renal failure if the kidney has physiologically significant renal artery stenosis (MIIMAC expert opinion).

U/S
There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

The radiation doses of radiopharmaceuticals used for renal scintigraphy are summarized in Table 4. As the table shows, the effective dose equivalent (weighted organ radiation doses) with 37 megabecquerels (MBq) of ^{99m}Tc-MAG3 (0.37 millisieverts [mSv]) or ^{99m}Tc-DTPA (0.33 mSv) is less radiation than a plain abdominal X-ray in adults (1.4 mSv).[3]

Table 4: Radiation Dose Estimates for the Radiopharmaceuticals Used for Post-Transplant Renal Scintigraphy[3]

Organ	Estimated Radiation Dose (mSv)			
	MAG3		DTPA	
	Bladder voiding every 4.8 hrs	Bladder voiding at 30 min. and every 4 hrs	Bladder Voiding Every 4.8 hrs	Bladder voiding at 30 min. and every 4 hrs
Kidneys	0.148	0.144	0.141	0.137
Ovaries	0.215	0.085	0.199	0.126
Bone marrow	0.037	0.018	0.055	0.044
Bone surface	0.52	0.025	0.081	0.067
Testes	0.148	0.592	0.141	0.089
Urinary bladder wall	4.440	1.665	3.478	1.924
Uterus	0.481	0.189	0.407	0.244
Total body	0.052	0.024	0.067	0.048
Effective dose equivalent	**0.370**	**0.155**	**0.329**	**0.199**

DTPA = diethylenetriamine pentaacetic acid; hrs = hours; MAG3 = mercaptoacetyl triglycine; min. = minutes; mSv = millisevert.

Return to Summary Table.

CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of imaging tests for post-transplant renal scintigraphy are presented by imaging modality. A summary of the availability of personnel required for the conduct of methods for post-transplant renal scintigraphy, by renal scan or any of the alternative imaging modalities, is provided in Table 5.

Renal scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of renal scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct renal scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic computed tomography (CT) scans, MRI, and U/S should be diagnostic radiologists[35] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial licence.[46]

Medical radiation technologists must be certified by the Canadian Association of Medical Radiation Technologists or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted part-time) should be available for the installation, testing, and ongoing quality control of nuclear medicine equipment.[46]

U/S
Sonographers (or ultrasonographers) should be graduates of an accredited School of Sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[35] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[35]

Table 5: Medical Imaging Professionals in Canada[35]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**MRTs**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	–	–	NR	0
NT	0	0	26	1	NR	0
NU	0	0	–	–	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; MRT = medical radiation technologist; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

Return to Summary Table.

CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 6 provides an overview of the availability of equipment required for post-transplant renal scintigraphy. Data for nuclear medicine cameras (including single-photon emission computed tomography [SPECT]) are current to January 1, 2007. The number of SPECT/CT scanners is current to January 1, 2010. Data were not available for U/S.

Table 6: Diagnostic Imaging Equipment in Canada[35,47]		
	Nuclear Medicine Cameras	**SPECT/CT Scanners**
Number of devices	603[35]	96[47]
Average number of hours of operation per week (2006-2007)[35]	40	n/a
Provinces and Territories with no devices available	YT, NT, NU	PEI, YT, NT, NU

NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; SPECT/CT = single-photon emission computed tomography/computed tomography; YT = Yukon.

Renal scintigraphy

For renal scans, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[35] In 2007, the latest year for which data are available, the average time for renal scintigraphy at McGill University Health Centre hospitals was 13 days. However, the wait times were reported to be less than one day for emergency cases.[36]

U/S
U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[37]

Return to Summary Table.

CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of renal scintigraphy and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 7), the cost of renal scintigraphy with ^{99m}Tc-based radioisotopes is $241.95. U/S is a minimally less costly alternative.

Table 7: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services under the *Health Insurance Act* (September 2011)[48]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
Renal scintigraphy				
J835	Computer-assessed renal function — includes first transit	135.10	73.00	208.10
Maintenance fees — from global budget		33.85		33.85
	TOTAL	168.95	73.00	**241.95**
U/S				
J205	Doppler evaluation of organ transplantation (arterial and/or venous)	22.60	18.70	41.30
Maintenance fees — from global budget		3.30		3.30
	TOTAL	25.90	18.70	**44.60**

Prof. = professional; Tech. = technical; U/S = ultrasound.

Return to Summary Table.

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APPENDIX
Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE <1946 to March 14, 2011>
Date of Search:	March 14, 2011
Alerts:	Monthly search updates began March 14, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	English language No date limits for systematic reviews; Publication years 1996-March 14, 2011 for primary studies; Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Multi-database Strategy	
#	**Searches**
1	Kidney Transplantation/
2	((kidney* or renal*) adj5 (transplant* or graft* or allograft*)).ti,ab.
3	1 or 2
4	Technetium/
5	exp Technetium Compounds/
6	exp Organotechnetium Compounds/

Multi-database Strategy	
7	exp Radiopharmaceuticals/
8	(Technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc*).tw,nm.
9	Radionuclide Imaging/ or Perfusion Imaging/
10	radionuclide imaging.fs.
11	radioisotope*.mp.
12	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
13	Tomography, Emission-Computed, Single-Photon/
14	(single-photon adj2 emission*).ti,ab.
15	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
16	((Renal* or kidney*) adj2 (imag* or scan*)).ti,ab.
17	(MAG3 or Mercaptoacetyltriglycine or Mertiatide or TechneScan or Mercaptoacetylglycylglycylglycine or Mercaptoacetyltriglycine).ti,ab.
18	125224-05-7.rn.
19	or/4-18
20	meta-analysis.pt.
21	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
22	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
23	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
24	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
25	(data synthes* or data extraction* or data abstraction*).ti,ab.
26	(handsearch* or hand search*).ti,ab.
27	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
28	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
29	(meta regression* or metaregression* or mega regression*).ti,ab.
30	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
31	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
32	(cochrane or health technology assessment or evidence report).jw.
33	or/20-32
34	3 and 19 and 33
35	34
36	limit 35 to english language
37	exp "Sensitivity and Specificity"/
38	False Positive Reactions/
39	False Negative Reactions/
40	du.fs.
41	sensitivit*.tw.
42	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti,ab.
43	(predictive adj4 value*).tw.
44	Comparative Study.pt.

Multi-database Strategy	
45	(Validation Studies or Evaluation Studies).pt.
46	Randomized Controlled Trial.pt.
47	Controlled Clinical Trial.pt.
48	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
49	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
50	Multicenter Study.pt.
51	(random* or sham or placebo*).ti.
52	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
53	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
54	(control* adj3 (study or studies or trial*)).ti.
55	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
56	(allocated adj "to").ti.
57	Cohort Studies/
58	Longitudinal Studies/
59	Prospective Studies/
60	Follow-Up Studies/
61	Retrospective Studies/
62	Case-Control Studies/
63	Cross-Sectional Study/
64	(observational adj3 (study or studies or design or analysis or analyses)).ti.
65	cohort.ti.
66	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
67	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
68	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
69	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
70	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
71	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
72	(population adj3 (study or studies or analysis or analyses)).ti.
73	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
74	or/37-73
75	3 and 19 and 74
76	75 not case reports.pt.
77	exp animals/
78	exp animal experimentation/
79	exp models animal/
80	exp animal experiment/
81	exp vertebrate/
82	or/77-81
83	exp humans/
84	82 not 83
85	76 not 84
86	85
87	limit 86 to yr="1996 -Current"

Multi-database Strategy	
88	87
89	limit 88 to english language

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 2, 2011;	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE	
Dates for Search:	March 10 to 15, 2011
Keywords:	Included terms for kidney transplantation and radionuclide imaging
Limits:	English language

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Definitions

Acute tubular necrosis (ATN): A term to describe the functional cellular injury of the renal tubules due to ischemia.

The Banff working classification of kidney transplant pathology: In this schema, intimal arteritis and tubulitis are the principal lesions indicative of acute rejection. Glomerular, interstitial, tubular, and vascular lesions of acute rejection and "chronic rejection" are defined and scored 0 to 3+ to produce an acute and/or chronic numerical coding for each biopsy. Arteriolar hyalinosis (an indication of cyclosporine toxicity) is also scored. Principal diagnostic categories, which can be used with or without the quantitative coding, are: (1) normal, (2) hyperacute rejection, (3) borderline changes, (4) acute rejection (grade I to III), (5) chronic allograft nephropathy ("chronic rejection") (grade I to III), and (6) other.

Effective dose equivalent: The effective dose equivalent is a way of converting the actual complicated process of radioactive intake into a simplified concept of a uniform whole-body dose;, i.e. an equivalent of what an actual localized dose means to the overall body.

Megabecquerel (MBq): The becquerel (symbol Bq), named after Henri Becquerel, a Noble Prize winner for discovering radioactivity, is a unit of radioactivity. One Bq is defined as the activity of a quantity of radioactive material in which one nucleus decays per second. MBq is equal to 10^6 Bq.

Millisievert (mSv): The sievert (symbol Sv), named after Rolf Sievert, a Swedish medical physicist, is a unit of dose equivalent. It shows the biological effects of radiation, as opposed to the physical aspects, which are characterized by the absorbed dose. A mSv is one-thousandth of a sievert.

The quantitative parameters used by the included studies for interpretation of scintigraphic results:

- Hilson's perfusion index is the area under the arterial curve to peak divided by the area under the renal curve × 100
- Peak-to-plateau ratio is the peak activity divided by the plateau activity on the renal perfusion curve
- Uptake is the ratio of kidney activity to background activity
- Retention [R_{20}] is the percentage of peak kidney activity retained at 20 minutes
- T_{peak} is the time at the peak of the renal perfusion curve.

Appendix 4: Description of the Studies Included to Assess the Diagnostic Accuracy of Renal Scintigraphy and Its Alternatives

Kim et al. (2005)[33]

This prospective study was conducted to compare the feasibility and value of harmonic ultrasound (U/S) with a microtubule contrast agent, with ^{99m}Tc-DTPA renal scintigraphy, in evaluation of post-transplant renal perfusion abnormalities. The study included 100 renal transplant recipients who underwent both renal scintigraphy and harmonic U/S. The results of both tests were evaluated quantitatively, using the time at the peak of the renogram curve (T_{peak}), with a cut-off point of 35 seconds. Compared to renal scintigraphy, harmonic U/S was found to have a sensitivity of 85% and a specificity of 90%. Based on their findings, the authors suggested harmonic U/S with a microtubule contrast agent as an effective sonographic technique for the evaluation of transplanted kidney perfusion.

Isiklar et al.(1999)[18]

This prospective study was conducted to compare the diagnostic accuracy of renal scintigraphy and Doppler U/S with that of core needle biopsy in detecting renal transplant dysfunction. Twenty-nine adult transplant recipients were included in the study. ^{99m}Tc-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA) was used as the radiotracer for renal scintigraphy, and Hilson's perfusion index was used for quantitative evaluation of perfusion of the renal cortex. The results of the study (see Table 8 in Appendix 5) showed the sensitivity and specificity of renal scintigraphy to be 59% and 57%, respectively. Power Doppler U/S was more sensitive than renal scintigraphy in the diagnosis of transplanted kidney perfusion impairment. However, both modalities had similar specificities. The authors concluded that power Doppler U/S can be used as a simple, repeatable, and rapidly analyzed method with acceptable sensitivity to investigate perfusion abnormalities in renal transplant recipients.

Aktas et al. (1998)[17]

This retrospective study was performed with the aim of evaluating the sensitivity of renal scintigraphy, as well as gray-scale and Doppler U/S, in the diagnosis of acute renal transplant rejection. Renal scintigraphy and both U/S examinations were performed in all 26 study participants within 48 to 72 hours. Scintigraphic images were acquired after injection of bolus ^{99m}Tc-DTPA. Time-activity curves were generated, and Hilson's perfusion index (perfusion phase), uptake value, and retained activity were used for quantitative evaluation of the kidney perfusion and function. Resistive index was used as a quantitative parameter in evaluation of the U/S results (Appendix 5, Table 8). Core needle biopsies with U/S guidance were conducted in all patients and the results were used as the standard of reference. The diagnosis of acute transplant rejection by biopsy was based on Banff classification. The authors regarded grade I and grade IIA rejections as low-grade and grade IIB and grade III rejections as high grade acute rejection. The sensitivity of renal scintigraphy was 45% to 85% for low-grade and 88% to 100% for high-grade rejections. The overall sensitivity of renal scintigraphy was higher than that of gray-scale and Doppler U/S examinations for both low- and high-grade acute rejections. The report did not include any conclusion or recommendations regarding the use of these modalities.

Delaney (1993)[24]

This cohort study evaluated patients both prospectively (111 episodes) and retrospectively (39 episodes) in order to compare efficacy and costs of U/S, renal scan, and fine-needle aspiration biopsy (FNAB). At a single institution, over a 12-month period, 150 episodes of allograft dysfunction in 128 renal transplant recipients were evaluated. At least three of four tests (core biopsy, FNAB, Doppler U/S, and renal scintigraphy) were performed on each patient prior to treatment and within 24 hours of deteriorating renal function. Core biopsy was performed on 106 occasions in 92 patients. Based on a combination of response to antirejection therapy and allograft histology, the study authors determined various causes of renal dysfunction. The sensitivities reported were based on the diagnosis of acute rejection, which was confirmed by beneficial response to acute antirejection therapy. Renal scanning was the most sensitive (70%) when compared with FNAB (52%) and U/S (43%). The authors recommended an initial U/S or renal scan, followed by core biopsy, as the most productive approach to diagnosis.

Appendix 5: Diagnostic Accuracy

Table 8: Diagnostic Accuracy of Renal Scintigraphy and Its Alternatives

Study (year)	Study Design	Population/ Condition (sample size)	Standard of Reference	Test	Parameters Evaluated* (cut-off-point for diagnosis)	Diagnostic Accuracy		
						Sensitivity	Specificity	Other
Aktas (1998)[17]	Retrospective observational study	Adults/ acute renal transplant rejection (26)	Renal biopsy	RS (^{99m}Tc-DTPA)	Perfusion phase: Hilson's PI (> 100)	45% to 57% (LGR) 88% (HGR)	–	–
					Parenchymal phase: Uptake (< 3)	55% to 71% (LGR) 100% (HGR)	–	–
					Retention [R20] (> 60%)	64% to 85% (LGR) 100% (HGR)		
				U/S (gray scale)	Resistive index (>0.71)	36% to 57% (LGR) 75% (HGR)	–	–
				U/S (Doppler)		45% to 71% (LGR) 88% (HGR)	–	–
Isiklar (1999)[18]	Prospective cohort	Adults/ renal transplant dysfunction (29)	Renal biopsy	RS (^{99m}Tc-DTPA)	Hilson's PI (> 100)	59%	57%	Ac = 58% PPV = 81% NPV = 30% Prevalence† = 75%
				U/S (power Doppler)	–	81%	57%	Ac = 75% PPV = 85% NPV = 50% Prevalence = 75%

Table 8: Diagnostic Accuracy of Renal Scintigraphy and Its Alternatives								
Study (year)	**Study Design**	**Population/ Condition (sample size)**	**Standard of Reference**	**Test**	**Parameters Evaluated* (cut-off-point for diagnosis)**	**Diagnostic Accuracy**		
						Sensitivity	**Specificity**	**Other**
Kim (2005)[33]	Prospective cohort	Adults/ impaired renal transplant perfusion	RS (DTPA)	Harmonic‡ U/S	T(peak)	85%	90%	r = 0.74 (P = 0.0001)
Delaney (1993)[24]	Prospective cohort (28% of patents were evaluated retrospectively)	Patients with renal transplant dysfunction (140) Acute rejection (60)	Renal biopsy	FNAB	Corrected increment ≥ 3.5	52%	–	–
				RS (^{99m}Tc-DTPA and OIH)	Delayed and/or decreased ^{99m}Tc-DTPA perfusion or OIH excretion	70%	–	–
				U/S (Doppler)	Resistive index (≥ 0.72)	43%	–	–

Ac= accuracy; FNAB= fine-needle aspiration biopsy; HGR= high-grade rejection (grades IIB and III of Banff classification); LGR= low-grade rejection (grades I and IIA of Banff classification); ^{99m}Tc DTPA= ^{99m}Tc-diethylenetriamine pentaacetic acid; MAG3= ^{99m}Tc-mercaptoacetyl triglycine; NPV= negative predictive value; OIH= ^{131}I o-iodohippurate; PI= perfusion index; PPV= positive predictive value; r = correlation coefficient; RS= renal scintigraphy; U/S = ultrasound.

† Calculated based on data provided in the article

‡ Harmonic US: U/S with microtubule contrast agent

***** Quantitative parameters:

Hilson's perfusion index — the area under the arterial curve to peak divided by the area under the renal curve × 100

Peak-to-plateau ratio — peak activity divided by the plateau activity on the renal perfusion curve

Uptake — the ratio of kidney activity to background activity

Retention [R_{20}] — the percentage of peak kidney activity retained at 20 minutes

T_{peak} — the time at the peak of the renal perfusion curve.

APPENDIX 2.14

INDICATION OVERVIEW

Some drugs used to treat cancer have been associated with cardiotoxicity (damage to the heart). These agents include anthracyclines (e.g., daunomycin, doxorubicin, epirubicin, idarubicin, and mitoxantrone), trastuzumab (Herceptin) and imatinib (Gleevec).

Anthracycline-related cardiotoxicity is from a cumulative dose of the agent and usually begins as asymptomatic failures in the pumping of the heart that can progress to heart failure.[1] It can present as abnormalities on electrocardiograms, irregular heartbeat, pericarditis-myocarditis syndrome (inflammation of the heart muscle or pericardium), or an increase in a brain peptide that is a marker of increased cardiac filling pressures. It is more common in elderly patients.[1]

Trastuzumab-related cardiotoxicity is not related to cumulative dose and is usually reversible with treatment discontinuation.[2] It usually presents as an asymptomatic decrease in left ventricular ejection fraction (LVEF), leading less often to heart failure. Trastuzumab therapy is often used in patients who have already undergone anthracycline therapy regiments and it is therefore sometimes unclear which agent is responsible for cardiotoxicity.

Imatinib-related cardiotoxicity is less common than the previous agents and is likely mediated by the inhibition of the c-ABL protein.[3]

Nuclear imaging for cardiotoxicity checks cardiac function prior to and during treatment to determine if dose adjustments need to be made or other alternative treatment options explored.[1,2,4] A common nuclear medicine heart test is the radionuclide angiogram (RNA). This scan measures the amount of blood ejected from the ventricle with each heart beat (ejection fraction). For example, if the left ventricle ejects 60% of its blood volume with each beat, the LVEF is 0.6 (normal is 0.5 or greater).

Based on a review of tests for monitoring doxorubicin-induced cardiomyopathy,[5] congestive heart failure (CHF) is usually dose-related and rarely occurs at cumulative doxorubicin doses below 450 mg/m^2. CHF associated with low-dose chemotherapy likely occurs in patients with underlying risk factors. In a review by Appel et al.,[6] the incidence of heart failure rises dramatically as cumulated dose rises. For doxorubicin doses of 400 mg/m^2, incidence of CHF is reported to be 3% and rises to 18% with doses of 700 mg/m^2. For epirubicin, the incidence increased from 4% at 900 mg/m^2 to 15% at 1,000 mg/m^2.[6]

Based on pediatric guidelines[7] for cardiac monitoring, it is recommended that evaluations should be done at baseline (prior to administration of agents), and then before every other course if the dose of doxorubicin is less than 300 mg/m^2, or before every course when the dose is greater than 300 mg/m^2. After therapy has been terminated, RNA evaluations should be done at one year post-therapy and then every five years. Echocardiography (Echo) should be done at one year post-therapy and then every two years when values are normal, and every year when values are abnormal.

Population: Adult and pediatric patients undergoing chemotherapy with antineoplastic drugs known to cause cardiotoxicity.

Intervention: Radionuclide angiography (RNA). Synonyms include gated blood pool scan (GBPS), radionuclide ventriculography (RVG), radionuclide cineangiography (RNCA), and equilibrium radionuclide angiography (ERNA). The term RNA will be used throughout this report.

Red blood cells are labelled with technetium-99m (^{99m}Tc). Radioactivity is measured with a gamma camera suitably positioned over the patient's chest as the radioactive blood flows through the large vessels and heart. The number of counts recorded at any time is proportional to the amount of blood radioactivity and these counts are proportional to the left ventricular (LV) volume. RNA accumulates data over a thirty-minute period. LV counts at end diastole and at end systole or throughout the cardiac cycle are measured by constructing LV regions of interest (ROI). The measured LV counts within these LV ROIs are corrected for background scatter (BkCorr). The LVEF = ([BkCorr end-diastolic counts – BkCorr end systolic counts]/BkCorr end-diastolic counts) x 100.[8]

Comparators: For this report, the following diagnostic tests are considered as alternatives to RNA:

- *Echocardiography (*Echo*)*
- *Cardiovascular magnetic resonance imaging (cardiac MRI or CMRI).*

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging, including RNA, and cardiotoxicity from chemotherapy.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. Retrieval was limited to the human population. The search was also limited to English language documents, with no publication date limits. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

There were 32 potential clinical articles identified through the MA/SR/HTA filtered search, and 13 were subjected to full text review. There were no meta-analyses of the diagnostic accuracy of RNA.

There were 243 potential articles identified through searching the primary diagnostic accuracy literature, of which 48 were subjected to full-text screening. Three articles comparing the diagnostic accuracy of LVEF measured with RNA and Echo were retained.[9-11] An additional seven articles identified through searching primary studies provided information pertaining to the following criteria: affected population;[7] mortality;[5,12] morbidity and quality of life;[5,13,14] and diagnostic accuracy.[15,16] The remaining 18 citations were either articles found through searching the grey literature, articles from the targeted searches, or articles from the reference lists of the identified potential articles.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	Anthracyclines and some monoclonal antibody-based therapies can be cardiotoxic. These drugs are commonly used to treat breast cancer and lymphomas. An estimated 32,220 new cases of breast cancer of lymphoma are expected in Canada in 2011.[17] It is recognized that not all patients with these cancer types will receive these treatments. Based on the estimated new cases and assuming they will each undergo cardiac assessment at least once during their treatment, the size of the affected population would be more than 1 in 10,000 (0.01%) and less than 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	Based on the urgency classifications developed by the Saskatchewan Ministry of Health, an RNA scan should be performed within two to seven days of receiving the request for the test for patients requiring cardiotoxic therapy on an urgent basis (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). RNA for initial and serial LVEF in patients receiving cardiotoxic chemotherapy should be performed within eight to 30 days of receiving the request for the test (Saskatchewan Ministry of Health: unpublished data, 2011). Based on findings from the assessment, the dose can be reduced, and concurrent administration of cardioprotective agents can be initiated to reduce the negative effects of the anthracycline drugs.[18] No literature describing the urgency of cardiac imaging post-treatment was identified. Obtaining the test results in the appropriate timely manner has moderate impact on patient management.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	*During treatment:* Symptomatic CHF is the most serious complication of anthracycline-based chemotherapy.[19] The incidence of CHF is between 5% and 48%, depending on the cumulative dose received.[19] If early LVEF reduction is unrecognized and untreated, continued treatment with anthracyclines may lead to irreversible severe CHF and may be fatal.[5] *Post-treatment:* Reporting on the epidemiology of cardiotoxicity in children who have received athracycline compounds shows that the risk of mortality from cardiac-related events is eight times higher for long-term cancer survivors than for the normal population.[18] The risk of anthracycline-induced clinical heart failure 15 to 20 years after the start of therapy is 4% to 5%.[18]

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
		Based on the limited information available, diagnostic imaging results are assumed to have a minimal impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	If early LVEF reduction is unrecognized and untreated, additional therapy may lead to irreversible, severe CHF, impacting patient morbidity and quality of life.[5] According to the United States national catalogue of preference-based, health-related quality of life scores,[20] the mean ratings of quality of life are lower in patients with CHF compared with age-matched adults without CHF. Based on the limited information available, diagnostic imaging results are assumed to have a moderate impact on morbidity and quality of life.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	No information regarding the patient acceptability of RNA was identified; however, with the assumption that the test is similar to other nuclear medicine tests, RNA is likely to be well-accepted. Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Echo is likely to be well tolerated by patients. Echo may be preferred by some patients, as there is no radiation exposure. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[21,22] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. RNA imaging with ^{99m}Tc radiolabelled tracers is: • minimally less acceptable than Echo • minimally less acceptable than MRI.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
7	**Relative diagnostic accuracy of the test**	One study reported that RNA identified a statistically significant larger proportion of patients with decreased LVEF compared with Echo,[10] and a second reported a slight underestimation of LVEF by Echo compared with RNA.[23] There is modest correlation of 2D TTE with CMRI, and a strong correlation between 3D TTE and RNA compared with CMRI. Based on the limited information available, the diagnostic accuracy of RNA imaging with ^{99m}Tc radiolabelled tracers: • is minimally better than Echo • has similar accuracy to that of MRI.
8	**Relative risks associated with the test**	**Non–radiation-related Risks** No information was identified regarding the non-radiation-related risks for patients undergoing RNA. No risks associated with Echo were identified. MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[24] Side effects of Gd include headaches, nausea, and metallic taste. The frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%), and the frequency of moderate reactions range is also rare (0.004% to 0.7%).[25] **Radiation-related Risks** Patients undergoing RNA are exposed to a radiation dose of 6.2 mSv.[26] The comparators (Echo and MRI) do not expose the patient to ionizing radiation. Overall, RNA imaging with ^{99m}Tc radiolabelled tracers is: • minimally less safe than Echo, • minimally less safe than MRI.
9	**Relative availability of personnel with expertise and experience required for the test**	*Expertise*: Sensitivity, specificity, and reproducibility of LVEF measures by Echo are strongly influenced by inter-observer variability whereas RNA is not. *Personnel*: In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic nuclear imaging, CT scans, MRI, and ultrasound should be diagnostic radiologists or nuclear medical physicians. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). Not all radiologists, nuclear medical physicians, nuclear cardiologists, or

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>cardiologists have the expertise to conduct ^{99m}Tc-RNA and all of its alternatives. For example, a 2002 report by the Canadian Cardiovascular Society reported that 43% of cardiologists do echocardiography.

Depending on the centre and assuming the necessary equipment is available, if ^{99m}Tc imaging using RNA is not available:
• more than 95% of the procedures can be performed in a timely manner using Echo
• 25% to 74% of the procedures can be performed in a timely manner using MRI.</td></tr>
<tr><td>**10**</td><td>**Accessibility of alternative tests (equipment and wait times)**</td><td>Nuclear medicine facilities with gamma cameras are required for RNA. As of January 1, 2007, there was an average of 18.4 nuclear medicine cameras per million people, with none available in the Yukon, Northwest Territories, or Nunavut.[27] SPECT/CT scanners were available in only five jurisdictions at that time: New Brunswick, Quebec, Ontario, Saskatchewan, and British Columbia.[27]

No information was found to identify how many echocardiography machines are available in Canada.

No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[28] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[27] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[29]

Depending upon the centre and assuming that the necessary expertise is available, if ^{99m}Tc imaging using RNA is not available:
• more than 95% of the procedures can be performed in a timely manner using Echo
• 25% to 74% of the procedures can be performed in a timely manner using MRI.</td></tr>
<tr><td>**11**</td><td>**Relative cost of the test**</td><td>According to our estimates, the cost of RNA with ^{99m}Tc-based radioisotopes is $330.40. Echo is a minimally less costly alternative; while MRI is moderately more costly than RNA with ^{99m}Tc-based radioisotopes.

<table>
<tr><th colspan="3">Relative costs</th></tr>
<tr><th>Test</th><th>Total costs ($)</th><th>Cost of test relative to ^{99m}Tc-based test ($)</th></tr>
<tr><td>RNA</td><td>330.40</td><td>Reference</td></tr>
</table>
</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses					
Criterion		**Synthesized Information**			
		Echo	150.55	-179.85	
		MRI	759.29	+428.89	

2D TTE = two-dimensional transthoracic echocardiography; 3D TTE = three-dimensional transthoracic echocardiography; CHF = congestive heart failure; CIHI = Canadian Institute for Health Information; CMRI = cardiac magnetic resonance imaging; Echo = echocardiography; Gd = gadolinium; LVEF = left ventricular ejection fractions; MRI = magnetic resonance imaging; PE = Prince Edward Island; RNA = radionuclide angiography; SPECT/CT = single-photon emission computed tomography/computed tomography; ^{99m}Tc = Technetium-99m;.

CRITERION 1: Size of affected population (link to definition)

Anthracyclines and some monoclonal antibody-based chemotherapy treatments can be cardiotoxic. These drugs are commonly used to treat breast cancer and lymphomas. An estimated 32,220 new cases of breast cancer of lymphoma are expected in Canada in 2011.[17] It is recognized that not all patients with these cancer types will receive chemotherapy. Some patients may undergo more than one cardiac assessment during his or her chemotherapy regimen.

After six years of therapy with anthracyclines, approximately 65% of children treated with a total dose in range between 228 mg/m^2 and 550 mg/m^2 have abnormalities in cardiac structure and function.[18] The risk of anthracycline-induced clinical heart failure 15 to 20 years after the start of therapy is 4% to 5%.[18]

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Based on the urgency classifications developed by the Saskatchewan Ministry of Health, RNA should be performed within two to seven days for patients requiring cardiotoxic chemotherapy on an urgent basis (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). The classifications also state that RNA for initial and serial LVEF in patients receiving cardiotoxic chemotherapy should be performed within eight to 30 days (Saskatchewan Ministry of Health: unpublished data, 2011).

The impact on the management of the condition or the effective use of health care resources is assumed to be greatest when the patient is first starting a potentially cardiotoxic treatment. That is when the chemotherapy dose can be reduced and concurrent administration of cardioprotective agents can be initiated to reduce the negative effects of the anthracycline drugs.[18]

No literature describing the urgency of cardiac imaging post-treatment was found.

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

Symptomatic CHF is the most serious complication of anthracycline-based chemotherapy.[19] The incidence is reportedly between 5% and 48%, depending on the cumulative dose received.[19] Based on a review of tests for monitoring doxorubicin-induced cardiomyopathy,[5] CHF rarely occurs at cumulative doxorubicin doses below 450 mg/m^2. CHF attributable to low-dose chemotherapy likely occurs in patients with underlying risk factors.[5] If early LVEF reduction is unrecognized and untreated, additional anthracycline therapy may lead to irreversible severe CHF and may be fatal.[5]

Ruggiero et al.[18] reviewed the literature and analyzed the pharmacological features and clinical data on anthracycline compounds. Reporting on the epidemiology of cardiotoxicity in children, the authors found that the risk of mortality from cardiac-related events is eight times higher for long-term cancer survivors than for the normal population.[18] The risk of anthracycline-induced clinical heart failure 15 to 20 years after the start of therapy is 4% to 5%.[18]

The Childhood Cancer Survivor Study is a retrospective cohort study designed to study late effects among long-term survivors of childhood cancers.[30] The study followed 20,227 survivors for a total of 208,947 person-years and reported 2,030 deaths.[30] Eighty-three deaths (4.5% of study deaths) were attributed to cardiotoxicity.[30] Relative to the American population, Mertens et al. found the cancer survivors in the Childhood Cancer Survivor Study to be 8.2 times more likely to die from cardiac events.[30]

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

If early LVEF reduction is unrecognized and untreated, additional anthracycline therapy may lead to irreversible, severe CHF, impacting patient morbidity and quality of life.[5] According to the United States national catalogue of preference-based, health-related quality of life scores developed by Sullivan and Ghushchyan ,[20] the mean EQ-5D score reported by patients with chronic heart failure (n = 284, mean age = 71) is 0.636, compared with a mean score of 0.790 among adults aged 70-79. The EQ-5D is a well-validated measure of five dimensions of health status (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression).

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CRITERION 5: Relative impact on health disparities (link to definition)

The risk of cardiotoxicity following breast cancer treatment has been associated with increased age, pre-existing conditions, and black race.[19,31] A 2007 retrospective analysis of 43,338 women aged 66 to 80 years found an increased risk of cardiotoxicity among the 71- to 80-year-old patient group versus the 66- to 70-year-old patient group, but did not find an increased risk of heart failure among anthracycline-treated women aged 71 to 80 when compared with non-anthracycline treated women of the same age.[19] The same study found that black patients had a 49% higher risk of developing CHF than did white patients; they were also more likely to receive adjuvant anthracycline chemotherapy.[19] The unavailability of ^{99m}Tc or the replacement with an alternative imaging modality is not likely to worsen any of the disparities mentioned here.

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

RNA
No information regarding the patient acceptability of RNA was identified; however, with the assumption that the test is similar to other nuclear medicine tests, RNA is likely to be well-accepted. Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent.

Echo
This test is likely to be well-tolerated by patients. Echo may preferred by some patients, as there is no radiation exposure.

MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension with MRIs and 5% to 10% endure some severe psychological distress, panic, or

claustrophobia.[21,22] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

A literature search for systematic reviews and primary studies evaluating the diagnostic accuracy of RNA, relative to its comparators Echo and MRI, found three studies (published in 2001, 2006, and 2010). A 2009 review article by Alterna et al.[23] noted that the measurement of LVEF with RNA and Echo can underestimate actual cardiac damage because the reserve of the myocardium facilitates ventricular output, even in the presence of damaged muscle cells. The authors described the evidence supporting the monitoring of cardiovascular effects during and after chemotherapy as being of medium quality, and suggested a need for new methods for detecting and monitoring cardiotoxicity of chemotherapy.[23]

Walker et al.[11] conducted a cohort study (2010) to assess the consistency of RNA scans, two-dimensional transthoracic echocardiography (2D TTE) and three-dimensional transthoracic echocardiography (3D TTE) for determining LVEF, in comparison with cardiac magnetic resonance imaging (CMRI). The study population consisted of 50 breast cancer patients undergoing adjuvant trastuzumab therapy, with a mean age of 52.[11] The four imaging examinations were conducted prior to initiation of treatment, after six months, and after 12 months.[11] The results, measured in terms of mean differences in LVEF (%) and correlation coefficients, are reported in Table 2.[11] There was a modest correlation between 2D TTE and CMRI, while 3D TTE and RNA were more strongly correlated with CMRI.[11]

Table 2: Mean Difference in LVEF (%) and Correlation Coefficients by Imaging Modality With CMRI as the Reference Standard *

	2D TTE	Correlation Coefficient	3D TTE	Correlation Coefficient	RNA	Correlation Coefficient
Baseline	5.24 (4.9)	0.31	–1.1 (2.3)	0.91	–0.52 (2.6)	0.88
6 month follow-up	–0.56 (7.7)	0.53	–1.1 (1.9)	0.97	–0.86 (2.0)	0.97
12 month follow-up	–3.7 (6.1)	0.42	–1.5 (2.3)	0.90	–0.3 (2.2)	0.87

2D TTE = two-dimensional transthoracic echocardiography; 3D TTE = three-dimensional transthoracic echocardiography; CMRI = cardiac magnetic resonance imaging; LVEF = left ventricular ejection fraction; RNA = radionuclide angiography.
* Values are mean difference (standard deviation)

A 2006 study conducted in Turkey aimed to evaluate the sensitivity of RNA and Echo in a cohort of 21 pediatric cancer patients (median age of 6.9 years, range 1.8 to 14 years).[9] Both techniques (RNA and Echo) were performed before the first course of chemotherapy and again in the three months following therapy.[9] After the first course of chemotherapy, RNA detected six (29%) patients with a decreased LVEF, compared with three (14%) patients with decreased LVEF with Echo ($p = 0.003$).[9] Both baseline and post-chemotherapy ejection fraction measurements were higher with Echo (Table 3), but the difference was only statistically significant after treatment.[9] According to this study of a relatively small sample size, RNA appears to be more sensitive in detecting cardiac dysfunctions compared with Echo.[9]

Table 3: Characteristics of Cardiac Function Measured by Echo and RNA[9]			
	Echo	**RNA**	***P* value**
Baseline EF (%) mean ± SD (range)	72 ± 4 (65-80)	64 ± 9 (50-79)	0.649
EF after chemotherapy mean ± SD (range)	68 ± 11 (20-79)	58 ± 10 (32-74)	0.005
No. of patients with decreased EF (%)	3 (14%)	6 (29%)	0.003

Echo = Echocardiography; EF = ejection fraction; RNA = radionuclide angiography; SD = standard deviation.

A 2001 prospective study of 28 adult patients with lymphoma compared Echo and RNA in the monitoring of left ventricular systolic function.[10] Nousiainen et al.[10] measured patient LVEF at baseline, and at cumulative doses of 200, 400, and 500 mg/m^2 doxorubicin, using RNA and Echo. A decrease in LVEF of more than 10% units and below 50% was observed in 10 patients (36%) by RNA, in three patients (11%) with M-mode Echo, and five patients (19%) using 2D TTE.[10] The authors also reported that the M-Mode Echo gave a mean of 12% LVEF units higher than RNA.[10] The conclusion noted that the agreement between results with Echo and RNA is suboptimal, and therefore guidelines based on the use of RNA cannot be applied to Echo.[10]

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

RNA
No information was identified regarding non–radiation-related risks for patients.

Echo
Three relatively large studies — with sample sizes of 42,408 patients (2009),[32] 26,774 patients (2009),[33] and 5069 patients (2008)[34] — compared cardiac outcomes (non-fatal myocardial infarction or death) between patients who underwent contrast-enhanced Echo with patients who had an Echo without contrast. All three studies concluded that the risk of an adverse event is low and is no different than that of patients who received no contrast. No additional risks associated with Echo were identified.

MRI
MRI is contraindicated in patients with metallic implants including pacemakers.[35] MRI is often used in conjunction with the contrast agent gadolinium (Gd). Some patients may experience an allergic reaction to the contrast agent (if required) which may worsen with repeated exposure.[24] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*[25] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[25]

Radiation-related Risks

Among the modalities to assess chemotherapy-induced cardiotoxicity, RNA is the only one to expose the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 4.

Table 4: Effective Radiation Doses for Various Imaging Tests

Test	Effective Radiation Dose (mSv)
RNA	6.2[26]
Average background dose of radiation per year	1-3.0[36-38]

Echo = Echocardiography; MRI = magnetic resonance imaging; mSv = millisievert; RNA = radionuclide angiography

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to assess chemotherapy-induced cardiotoxicity are presented by imaging modality. A summary of the availability of personnel required for the conduct of methods to assess patients undergoing or having undergone chemotherapy, by RNA or any of the alternative imaging modalities, is provided in Table 5.

RNA

In Canada, physicians involved in the performance, supervision, and interpretation of cardiac nuclear imaging (specifically RNA using ^{99m}Tc-labelled radiotracers) should be nuclear medicine physicians with particular expertise in nuclear cardiology (nuclear cardiologists). For cardiac imaging, cardiologists provide much of the nuclear cardiology, cardiac MRI, and echocardiography services. According to the Canadian Medical Association (CMA), there are 1,149 practicing cardiologists in Canada (CMA, 2011).

Nuclear medicine technologists are required to conduct RNA scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities

In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound should be diagnostic radiologists[27] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists are also qualified if they are certified by a recognized certifying body and hold a valid provincial license.[39] According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011).

Medical radiation technologists must be certified by CAMRT or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification is ensured by the corporation responsible for service and by the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted part time) should be available for the installation, testing, and ongoing quality control of CT scanners, magnetic resonance scanners, and nuclear medicine equipment.[39]

Echo

Echocardiography is an ultrasound-based test. Cardiologists provide much of the Echo service. A 2002 report by the Canadian Cardiovascular Society reported that 43% of cardiologists do Echocardiography. According to the CMA, there are 1,149 practicing cardiologists in Canada (CMA, 2011). It is assumed that less than 500 of them do Echocardiography.

Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[27] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[27]

MRI

Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

Table 5: Medical Imaging Professionals in Canada, 2006[27]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	MRTs	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PE	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	0	0	NR	0
NT	0	0	26	1	NR	0
NU	0	0	0	0	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRT = medical radiation technologist; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PE= Prince Edward Island; ON = Ontario; QC = Quebec; YT = Yukon.
* this represents a total for all of the jurisdictions

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 6 provides an overview of the availability of equipment required to assess chemotherapy-induced cardiotoxicity. Data were not available for Echo.

Table 6: Diagnostic Imaging Equipment in Canada[27,28]

	Nuclear Medicine Cameras	MRI Scanners	SPECT/CT Scanners
Number of devices	603[27]	218[28]	96[28]
Average number of hours of operation per week (2006-2007)[27]	40	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	YT, NT, NU	PE, YT, NT, NU

NT = Northwest Territories; NU = Nunavut; PE = Prince Edward Island; YT = Yukon

RNA
Nuclear medicine facilities with gamma cameras are required for RNA imaging. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[27]

Echo
No information was found to identify how many Echocardiography machines are available in Canada.

MRI
No MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[28] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario with a national average of 71 hours.[27] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[29]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of RNA and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e. radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 7), the cost of RNA with ^{99m}Tc-based radioisotopes is $330.40. Echo is a minimally less costly alternative; while MRI is moderately more costly than RNA with ^{99m}Tc-based radioisotopes.

Table 7: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[40]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
RNA				
J813	Myocardial wall motion — studies with ejection fraction	138.60	82.25	220.85
J866	Application of SPECT (maximum 1 per examination)	44.60	31.10	75.70
Maintenance fees — from global budget		33.85		33.85
	TOTAL	217.05	113.35	**330.40**
Echo				
G570/G571	Complete study — 1 and 2 dimensions	76.45	74.10	150.55
	TOTAL	76.45	74.10	**150.55**
MRI				
X441C	MRI — thorax — multislice sequence		77.20	115.85
X445C (×3)	Repeat (another plane, different pulse sequence — to a maximum of 3 repeats)		38.65 (×3) = 115.95	115.95
X499	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40
X487	When gadolinium is used		38.60	38.60
X486	When cardiac gating is performed (must include application of chest electrodes and ECG interpretation), add 30%		89.14	89.14
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	373.00	386.29	**759.29**

3-D = three-dimensional; ECG = electrocardiogram; MRI = magnetic resonance imaging; prof. = professional; RNA = radionuclide angiogram; SPECT = single-photon emission computed tomography; tech. = technical.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc to an Alternative, or Comparing Between Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc to an Alternative, or Comparing Between Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	OvidSP
Databases:	Ovid Medline Ovid Medline In-Process & Other Non-Indexed Citations Ovid Medline Daily EBM Reviews - Cochrane Central Register of Controlled Trials EBM Reviews - Database of Systematic Reviews EBM Reviews - Database of Abstracts of Reviews of Effects EBM Reviews - NHS Economic Evaluation Database (NHSEED) EBM Reviews - Health Technology Assessments **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	February 2, 2011
Alerts:	Monthly search updates began February 2011 and ran until October 2011
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies
Limits:	English language Human population

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

MULTI-DATABASE STRATEGY	
Line #	**Searches**
	Filter: health technology assessments, systematic reviews, meta-analyses
1	meta-analysis.pt.
2	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/

3	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
4	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
5	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
6	(data synthes* or data extraction* or data abstraction*).ti,ab.
7	(handsearch* or hand search*).ti,ab.
8	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
9	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
10	(meta regression* or metaregression* or mega regression*).ti,ab.
11	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
12	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
13	(cochrane or health technology assessment or evidence report).jw.
14	(meta-analysis or systematic review).md.
15	or/1-14
	Filter: randomized controlled trials, and non-randomized studies
16	exp "Sensitivity and Specificity"/
17	False Positive Reactions/
18	False Negative Reactions/
19	du.fs.
20	sensitivit*.tw.
21	(predictive adj4 value*).tw.
22	Comparative Study.pt.
23	(Validation Studies or Evaluation Studies).pt.
24	Randomized Controlled Trial.pt.
25	Controlled Clinical Trial.pt.
26	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
27	Multicenter Study.pt.
28	(random* or sham or placebo*).ti.
29	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
30	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
31	(control* adj3 (study or studies or trial*)).ti.
32	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
33	(allocated adj "to").ti.

34	Cohort Studies/
35	Longitudinal Studies/
36	Prospective Studies/
37	Follow-Up Studies/
38	Retrospective Studies/
39	Case-Control Studies/
40	Cross-Sectional Study/
41	(observational adj3 (study or studies or design or analysis or analyses)).ti.
42	cohort.ti.
43	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
44	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
45	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
46	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
47	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
48	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
49	(population adj3 (study or studies or analysis or analyses)).ti.
50	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
51	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).ti,ab.
52	or/16-51
53	case reports.pt.
54	52 not 53
	Cardiotoxicity concept
55	cardiotoxic*.mp.
56	((cardio* or cardiac) adj toxic*).mp.
57	exp Heart Failure/
58	exp Ventricular Dysfunction/
59	exp Heart Diseases/ci [Chemically Induced]
60	exp Arrhythmias, Cardiac/ci [Chemically Induced]
61	exp Cardiomyopathies/ci [Chemically Induced]
62	(cardiomyopathy or heart failure or cardiac failure or myocardial failure).ti,ab,hw.
63	(cardiac function* adj2 (monitor* or assess*)).ti,ab,hw.
64	or/55-63
	Chemotherapy concept
65	(chemotherap* or chemo therap*).mp.

66	(anthracyclin* or non-anthracyclin* or nonanthracyclin* or antineoplastic*).mp.
67	(trastuzumab or Herceptin or imatinib or Gleevec or doxorubicin or Adriamycin or Myocet or Caelyx or Doxil or daunorubicin or DaunoXome or Cerubidine or idarubic* or Idamycin or epirubicin or Pharmorubicin or Ellence or mitoxantrone or Novantrone).mp.
68	(fluorouracil or 5-FU or 5-fluorouracil or Adrucil or Efudex or Carac or Fluoroplex).mp.
69	(valrubicin or Valtaxin or Valstar).mp.
70	or/65-69
	Radionuclide imaging concept
72	Technetium/
73	exp Technetium Compounds/
74	exp Organotechnetium Compounds/
75	exp Radiopharmaceuticals/
76	radioisotope*.mp.
77	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.
78	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
79	radionuclide imaging.fs.
80	exp Radionuclide Imaging/
81	Tomography, Emission-Computed, Single-Photon/
82	(single-photon adj2 emission*).ti,ab.
83	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
84	exp Radionuclide Angiography/
85	exp Radionuclide Ventriculography/
86	(radionuclide adj2 (ventriculograph* or angiograph* or angiocardiograph*)).ti,ab.
87	MUGA.ti,ab.
88	(MUGA or RNCA or ERNA).ti,ab.
89	(gated adj2 (blood pool or acquisition)).ti,ab.
90	((LVEF or left ventricular or ejection fraction) and radionucl*).ti,ab.
91	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
92	or/72-91
	Filter: Human (non-animals)
93	exp animals/
94	exp animal experimentation/
95	exp models animal/
96	exp animal experiment/
97	nonhuman/

98	exp vertebrate/
99	animal.po.
100	or/93-99
101	exp humans/
102	exp human experiment/
103	human.po.
104	or/101-103
105	100 not 104
	Results
106	64 and 70 and 92
107	106 not 105
108	Remove duplicates
109	Limit to English language [Limit not valid in CDSR,DARE,CCTR,CLCMR; records were retained]
110	15 and 109
111	54 and 109

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	February 2011
Keywords:	Included terms for cardiotoxicity from chemotherapy and diagnostic imaging including gated blood pool scans (MUGA) and comparators
Limits:	Publication dates last 10 years, human population

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

APPENDIX 2.15

INDICATION OVERVIEW

Avascular necrosis (AVN) is also known as osteonecrosis, aseptic necrosis, and ischemic necrosis.[1,2] AVN is a sequela of hypoxic (i.e., lack of oxygen delivery or uptake) ischemic cell death.[2] AVN can be roughly divided by etiologies, and the most common causes are post-traumatic (most commonly, the femoral head of hip, the humeral head of the upper arm, and the small bones of the wrist — i.e., scaphoid — and ankle — i.e., talus), spontaneous or idiopathic, drug- (steroid) or excessive alcohol consumption–induced, and metabolic/genetic (e.g., sickle cell anemia, Gaucher disease).[3] Although spontaneous or traumatic AVN can affect populations spanning from adolescents to the elderly, the underlying trauma or specific pattern of bone involvement does vary with age.[2] The most common complaint of patients with AVN is pain that eventually leads to a decrease in range of motion.[4]

Population: Patients with suspected acute or subacute AVN.

Intervention: Bone scanning (bone scintigraphy) using technetium-99m–labelled methylene diphosphonate (^{99m}Tc-MDP).

As with nuclear bone imaging for other indications, the radioisotope-labelled MDP is injected intravenously, and there is increased uptake of ^{99m}Tc where there is increased bone turnover or remodelling.[1,5] Early-phase AVN is characterized by decreased uptake of radiotracer, producing a “cold area” on the scan.[6] Once the reparative process begins, there is increased radiotracer uptake in the area surrounding the cold spot, a pattern commonly referred to as the “donut sign.”[6] Bone scanning is useful for early diagnosis and follow-up of osteonecrosis.[6]

Single-photon emission computer tomography (SPECT) is a more advanced imaging technique, again requiring a radioactive tracer (^{99m}Tc-MDP) and a gamma camera. With SPECT, a computer constructs detailed two- or three-dimensional images of areas inside the body where the radiotracer is taken up by the cells.[7] SPECT/CT hybrid technology, introduced in 1999, provides the functional information of a nuclear scan, and the anatomical detail of CT increases the specificity of bone scans by providing more discrete anatomic localization of identified radioactive tracer abnormalities.[7]

Comparators: For this report, magnetic resonance imaging (MRI) is considered to be the only alternative to ^{99m}Tc-MDP.

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test

- 9. Relative availability of personnel with expertise and experience required for the test
- 10. Accessibility of alternative tests (equipment and wait times)
- 11. Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records and daily updates via Ovid; The Cochrane Library via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and avascular necrosis.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies. No human limits were applied for systematic reviews. For primary studies, human limits were applied. The search was also limited to English language documents. No date limits were applied. Regular alerts were established to update the search until October 2011. See Appendix 2 for the detailed search strategies.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

The literature search identified 15 meta-analyses (MA) or systematic reviews (SR) or health technology assessments (HTAs), 18 clinical practice guidelines (CPGs), and 771 primary studies. Three of the MA/SR/HTAs, four CPGs, and 65 primary studies were reviewed in full text. Articles that were excluded based on abstract only did not address diagnostic imaging as it relates to the diagnosis of acute or subacute AVN.

Two of the SRs addressed issues beyond the scope of this report: methods of treatment for concurrent ipsilateral fractures of the hip and femoral shaft[8] and screening methods to identify newborns at risk for developmental dysplasia of the hip (DDH).[9] The third article, indexed as a SR, was in fact a primary study characterizing bisphosphonate-related osteonecrosis of the jaw (BRONJ) among patients receiving intravenous bisphosphonates and examining bone scanning findings that preceded manifestations of frank osteonecrosis of the jaw (ONJ).[10] The four CPGs identified in the database search were published in 2008 and 2009 and addressed BRONJ from a Canadian perspective.[11-14] The grey literature search identified a number of guidelines not found in the database search, including those by the American College of Radiology (ACR),[15] College of Physicians and Surgeons of Ontario (CPSO),[16-19] and the Canadian Protective

Chiropractic Association and l'Université du Quebec à Trois-Rivières.[20] The ACR Appropriateness Criteria for AVN of the hip can be found in Appendix 3.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	AVN has been described as a relatively common disease,[15,21] but an estimate as to the number of Canadians affected by this affliction has not been found. According to the American Academy of Orthopedic Surgeons, the annual incidence of AVN in the US is estimated at 10,000 to 20,000 (3.26-6.51/100,000).[22] A Japanese prognostic study reported that 11,400 patients sought medical care for idiopathic ONFH in 2004 (8.9/100,000).[23] Assuming the incidence rate in Canada is similar to that in the US and Japan, this corresponds to more than 1 in 10,000 (0.01%), and less than 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	According to the Saskatchewan Ministry of Health urgency classifications, MRI, a comparator of ^{99m}Tc-based bone imaging, should be completed within 2 to 7 days for patients with suspected AVN.[24] Early diagnosis and treatment increases the likelihood of joint preservation.[25] Imaging results have a moderate impact on the management of the condition or the effective use of health care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	The diagnosis of AVN does not affect patient life expectancy.[25] The consequences of not performing imaging tests should have no impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Delayed diagnosis of AVN can have a serious impact on a patient's quality of life.[26] Once radiographic changes occur (stage II), most joints will collapse within 6 to 24 months, if untreated.[27] At stage IV, the changes are irreversible.[28] Replacement of the femoral head may be considered at stage IV, and by stage V, total hip replacement is required.[28] The diagnostic imaging test results can have a moderate impact on morbidity or quality of life.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
6	**Relative acceptability of the test to patients**	*Bone scanning* Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent. *MRI* Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[29,30] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some. Overall, bone scanning with ^{99m}Tc-radiolabelled tracers is minimally less acceptable than MRI.
7	**Relative diagnostic accuracy of the test**	In some American centres, MRI has largely replaced radionuclide bone scanning because of its greater sensitivity (up to 100%).[15] The generalizability of this finding to Canadian centres is uncertain. Based on the available evidence, the diagnostic accuracy of bone scanning with ^{99m}Tc-radiolabelled tracers is minimally lower than that of MRI.
8	**Relative risks associated with the test**	**Non–radiation-related Risks** Several studies[31-34] reported mild adverse events with ^{99m}Tc-labelled tracers (e.g., skin reactions). MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[35] Side effects of Gd include headaches, nausea, and metallic taste. The frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%), and the range in frequency of moderate reactions is also rare (0.004% to 0.7%).[36] **Radiation-related Risks** Among the modalities to diagnose AVN, bone scanning exposes the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures is tabulated.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th colspan="2">Effective Doses of Radiation</th></tr>
<tr><th>Procedure</th><th>Average effective dose (mSv)</th></tr>
<tr><td>Bone scan</td><td>4.5-6.3[37-39]</td></tr>
<tr><td>MRI</td><td>0</td></tr>
<tr><td>Average background dose of radiation per year</td><td>1-3.0[40-42]</td></tr>
</table>
In general, bone scanning may be minimally less safe than MRI.
</td></tr>
<tr><td>**9**</td><td>**Relative availability of personnel with expertise and experience required for the test**</td><td>As of 2006 in Canada, there were 2,034 diagnostic radiologists; 221 nuclear medicine physicians; 12,255 radiological technologists (MRTs); and 1,781 nuclear medicine technologists available across Canada. Yukon, Northwest Territories, and Nunavut do not have the available personnel to perform and interpret tests to image avascular necrosis.

Assuming the necessary equipment is available, it is estimated that 75% to 94% of procedures could be performed in a timely manner using MRI.</td></tr>
<tr><td>**10**</td><td>**Accessibility of alternative tests (equipment and wait times)**</td><td>For bone scintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. No nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[7]

No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[43] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[7] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[44]

Depending on the centre and assuming that the necessary personnel and expertise is available, it is estimated that 25% to 74% of procedures could be performed in a timely manner using MRI.</td></tr>
</table>

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of whole body bone scan with ^{99m}Tc-based radioisotopes is $344.016. MRI is a minimally more costly alternative.

<table>
<tr><th colspan="3">Relative costs</th></tr>
<tr><th>Test</th><th>Total costs ($)</th><th>Cost of test relative to ^{99m}Tc-based test ($)</th></tr>
<tr><td>Bone scan</td><td>344.01</td><td>Reference</td></tr>
<tr><td>MRI</td><td>501.90</td><td>+157.89</td></tr>
</table>
</td></tr>
</table>

AVN = avascular necrosis; CIHI = Canadian Institute for Health Information; Gd = gadolinium; MRI = magnetic resonance imaging; MRT = radiological technologists; mSv = millisievert; ONFH = osteonecrosis of the femoral head; SPECT = single-photon emission computed tomography.

CRITERION 1: Size of affected population (link to definition)

According to a report produced by the Institute for Clinical Evaluative Sciences (ICES), there were 1,008 nuclear bone scans performed per 100,000 population in the province of Ontario in 2005-2006.[45] If this rate were applied to the Canadian population, we would expect 345,526 bone scans performed in Canada each year.

AVN has been described as a relatively common disease,[15,21] but an estimate as to the number of Canadians affected by this affliction has not been found. According to the American Academy of Orthopedic Surgeons, the annual incidence of AVN in the US is estimated at 10,000 to 20,000 (3.26-6.51/100,000).[22] A Japanese prognostic study reported that 11,400 patients sought medical care for idiopathic osteonecrosis of the femoral head (ONFH) in 2004 (8.9/100,000).[23] Basic extrapolation of these data to the Canadian setting provides an estimate of 1,098 to 2,197 new cases annually; however, the generalizability of these numbers to the Canadian population is uncertain.

The risk of a completely healthy individual developing AVN is estimated at less than one in 100,000, but there are specific populations who are more affected.[25] AVN affects between five and 29 per 100 renal transplant recipients and approximately 15 out of every 100 systemic lupus erythematosus (SLE) patients.[26,46] After post-traumatic intracapsular fractures of the femoral neck, the incidence of AVN is 15 to 80 per 100 post-traumatic intracapsular fractors of the femora neck.[26]

The incidence of specific forms of AVN has also been reported. Legg–Calvé–Perthes (LCP) disease is a form of idiopathic AVN affecting the femoral head in approximately 5.1 to 15.6 per 100,000 preadolescent children.[47]

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Timeliness
Interventions to preserve the joint are associated with better prognoses when the diagnosis of AVN is made early in the course of disease progression.[48] In more advanced stages of the disease, when more of the joint is damaged, it becomes less likely that the natural joint can be preserved.[25]

Urgency
According to the urgency classifications developed by the Saskatchewan Ministry of Health, MRI, a comparator of ^{99m}Tc-based bone scanning, should be completed within two to seven days for patients with suspected AVN in any joint or bone. (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011.)

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

The diagnosis of AVN does not affect patient life expectancy.[25] The consequences of not performing imaging tests, or not diagnosing the condition, will affect the patient's quality of life and morbidity, but should have no effect on mortality.

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Although the natural history of AVN has not been completely determined, it is recognized that delayed diagnosis of AVN can seriously affect patient morbidity and quality of life.[26] For example, the average age of diagnosis for AVN of the femoral head is less than 40 years, making preservation of the joints a priority.[1,49]

Steinberg et al.[28] have devised a quantitative system for staging AVN of the femoral head (Table 2). Their evaluation of more than 1,000 hips during a period of 12 years provides evidence that early diagnosis and treatment can greatly improve prognosis and reduce morbidity. Once radiographic changes occur (stage II), most joints will collapse within six to 24 months, if untreated.[27] By the time the patient has reached stage IV, the changes are irreversible.[28] Replacement of the femoral head may be considered at stage IV, but by stage V, total hip replacement is required.

Table 2: Criteria for Staging AVN of the Femoral Head[28]

Stage	Description
0	Normal or non-diagnostic radiograph, bone scan and MRI
I*	Normal radiograph, abnormal bone scan and/or MRI
II*	Abnormal radiograph showing “cystic” and sclerotic changes in the femoral head
III*	Subchondral collapse producing a crescent sign
IV*	Flattening of the femoral head
V*	Joint narrowing with or without acetabular involvement
VI	Advanced degenerative changes

AVN = avascular necrosis; MRI = magnetic resonance imaging.
*The extent or grade of involvement should also be indicated as A, mild; B, moderate; or C, severe.

Return to Summary Table.

CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

AVN affects primarily people with underlying health problems, such as recent trauma and associated fractures, cancer, or recent transplant recipients.[25] The risk of a completely healthy individual developing AVN is estimated at less than one in 100,000, but there are specific populations who are more affected.[25] AVN affects between five and 29 per 100 renal transplant recipients and approximately 15 out of every 100 SLE patients.[26,46] After post-traumatic intracapsular fractures of the femoral neck, the incidence of AVN is 15 to 80 per 100 post-traumatic intracapsular fractures of the femoral neck.[26] AVN is more common in men: the male-to-female ratio has been estimated at 8:1[1]; however, it is not clear which etiology this ratio refers to. The unavailability of ^{99m}Tc or the replacement with an alternative imaging modality is not expected to worsen these disparities.

Children
Radiography and bone scanning involve exposure to ionizing radiation. This can be a concern in testing pediatric patients, as the risk of radiation-induced cancer is shown to be two to three times greater in children and adolescents than in adult patients.[50] The most common form of AVN in children is idiopathic (Perthes disease) and the changes are almost always visible on x-ray by the time the patient presents. For the diagnosis of treatment-induced, multifocal AVN of bone in children, whole-body MRI has been proposed as a safer screening tool.[51]

Residents of rural and remote areas
When radiographs are normal but AVN is suspected clinically, the ACR recommends MRI to establish or exclude AVN.[15] If MRI is not available, as may be the case in smaller centres, bone scan or CT may be appropriate.[15] In rural and remote areas without access to these imaging modalities, it may not be possible to confirm the diagnosis of AVN until stage II disease. As later diagnosis is associated with poorer prognosis, residents of rural and remote areas may experience increased morbidity associated with AVN.
Return to Summary Table.

CRITERION 6: Relative acceptability of the test to patients(link to definition)

Bone scanning
Patients may have concerns about radiation exposure and the intravenous injection of radiopharmaceutical agent.

MRI
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as be bothered by the noise. This may be less of a problem with new MRI machines, if available (MIIMAC expert opinion). It has been reported that up to 30% of patients experience apprehension with MRIs and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[29,30] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

Return to Summary Table.

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Our review of the literature identified seven primary studies on the ability of bone scanning with ^{99m}Tc-MDP to correctly diagnose patients with AVN (sensitivity) and without AVN (specificity). No systematic reviews were identified.

Table 3 summarizes the study objectives, interventions compared, study results, and authors' conclusions of those studies published in the past 20 years.[46,52,53] All of the studies involved relatively small sample sizes (24 to 107 patients).

Table 3: Diagnostic Accuracy of Bone Scan Versus Comparators (Studies Published 1991–2011)

Author, Date	Objective	Population	Interventions	Results	Conclusions
Mont et al. 2008[53]	To investigate the utility of bone scanning in the diagnosis or screening of AVN.	48 patients presenting to 2 institutions who underwent simultaneous (within 3 months) radiographs, bone scans, and MRI studies for possible symptomatic AVN of the hip, knee,	BS vs. MRI Histological confirmation was obtained for each suspected lesion and this was considered the "gold standard."	163 lesions identified by MRI and histology (sensitivity of 100% for MRI, specificity not reported). 91/163 lesions were identified by bone scan (55.8% sensitivity, specificity not reported).	Bone scanning was observed to have lower sensitivity than MRI in diagnosing symptomatic AVN. This study does not support the use of bone scans as a diagnostic or screening tool for AVN.

Table 3: Diagnostic Accuracy of Bone Scan Versus Comparators (Studies Published 1991–2011)

Author, Date	Objective	Population	Interventions	Results	Conclusions
		shoulder, or ankle. Patients with traumatic lesions were excluded.			
Ryu et al. 2002[46]	To compare the diagnostic sensitivity of bone SPECT and MRI for the detection of early AVN of the femoral head in renal transplant recipients.	24 renal allograft recipients (14 men and 10 women, aged 26-65 y) — 48 femoral heads.	SPECT vs. MRI	32 femoral heads were confirmed as having AVN (core decompression in 13 and THR arthroplasty in 14 within 14 months after bone SPECT, 5 confirmed in clinical follow-up). SPECT detected AVN in all 32 true positives, but also falsely categorized 6 femoral heads as positive (sensitivity of 100%, specificity of 62%). MRI had a sensitivity of 66% and a specificity of 100%.	Bone SPECT is more sensitive than MRI in the detection of early AVN of the femoral heads after renal transplantation.
Sakai et al. 2001[52]	To determine whether ^{99m}Tc-MDP BS is useful for screening of non-traumatic ONK, which was a major affected site, secondary to the femoral head, among multiple AVN, in patients with non-traumatic ONFH.	214 knee joints in 107 patients with ONFH.	BS vs. MRI.	Sensitivity, specificity, and accuracy of BS in comparison with MRI ONFC (n = 86): Sens. 63, Spec. 71, Accuracy 68 ONFM (n = 32): Sens. 3, Spec. 98, Accuracy 84 ONTP (n = 2): Sens. 100, Spec. 81, Accuracy 81 ONTM (n = 21): Sens. 0, Spec. 99, Accuracy 89 ONP (n = 6): Sens. 0, Spec. 98, Accuracy 95	All ONK lesions showed focal increased bone uptake and did not show "cold in hot pattern," which was specific to ONFH. The authors concluded their results indicate that BS is useful in screening large ONK in patients with non-traumatic ONFH.

^{99m}Tc-MDP = technetium-99m methylene diphosphonate; AUC = area under the curve; AVN = avascular necrosis; BS = bone scanning; MRI = magnetic resonance imaging; ONFC = osteonecrosis of the femoral chondrocyles; ONFH = osteonecrosis of the femoral head; ONFM = osteonecrosis of the distal femoral metaphysis; ONK = osteonecrosis of the knee; ONTP = osteonecrosis of the tibial plateau; ONTM = osteonecrosis of the proximal tibial metaphysis; ONP = osteonecrosis of the patella; ROC = receiver operating characteristic; sens. = sensitivity; spec. = specificity; SPECT = single-photon emission computed tomography; SPECT/CT = single-photon emission computed tomography/computed tomography; THR = total hip replacement; vs. = versus.

Bone scanning using ^{99m}Tc-MDP

Bone scanning using ^{99m}Tc-MDP has been advocated as a useful diagnostic tool for patients with suspected AVN.[27,46,54,55] Particularly before the advent and adoption of MRI, bone scanning was considered a more sensitive diagnostic test than standard radiographs for early disease

detection.[15,27] A 2008 study by Mont et al. concluded that bone scanning has a low sensitivity for diagnosing symptomatic AVN, particularly for early-stage lesions, and joints other than the hip.[53] The 1989 study by Stulberg et al.[55] found that SPECT is more sensitive than planar bone scan.

MRI
According to the American College of Radiology,MRI has largely replaced radionuclide bone scanning because of its greater sensitivity (up to 100%).[15] The generalizability of these findings to the Canadian health care system is uncertain.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Bone scanning
Several studies[31-34] reported mild adverse events with ^{99m}Tc-labelled tracers (e.g., skin reactions).

MRI
MRI is contraindicated in patients with metallic implants including pacemakers.[18] MRI is often used in conjunction with the contrast agent gadolinium (Gd). Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[35] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*,[36] the frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[36]

Radiation-Related Risks

Among the modalities to diagnose AVN, only bone scanning exposes the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Table 5. As the table shows, bone scanning delivers larger doses of radiation than X-ray.

Table 5: Effective Doses of Radiation

Procedure	Average Effective Dose (mSv)
Bone scan	4.5-6.3[37-39]
MRI	0
X-ray	0.01-0.7[38]
Average background dose of radiation per year	1-3.0[40-42]

MRI = magnetic resonance imaging; mSv = millisievert.
* Based on 740 MBq injection at 6.1E-03 mSv/MBq

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (equipment and wait times) (link to definition)

Bone scintigraphy
In Canada, physicians involved in the performance, supervision, and interpretation of bone scans should be nuclear medicine physicians or diagnostic radiologists with training or expertise in nuclear imaging.[56] Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct bone scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities
In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic CT scans, MRI, and ultrasound should be diagnostic radiologists[7] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists are also qualified if they are certified by a recognized certifying body and hold a valid provincial licence.[56]

Medical radiation technologists (MRTs) must be certified by CAMRT or an equivalent licensing body.

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and by the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted part time) should be available for the installation, testing, and ongoing quality control of CT scanners, magnetic resonance scanners, and nuclear medicine equipment.[56]

MRI
Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

Table 6: Medical Imaging Professionals in Canada, 2006[7]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	MRTs	Nuclear Medicine Technologists	Medical Physicists
NL	46	3	263	15	NR
NS	71	5	403	71	NR
NB	47	3	387	55	NR
PE	7	0	57	3	0
QC	522	90	3,342	460	NR
ON	754	69	4,336	693	NR
MB	58	8	501	42	NR
SK	61	4	359	36	NR
AB	227	18	1,229	193	NR
BC	241	21	1,352	212	NR

Table 6: Medical Imaging Professionals in Canada, 2006[7]					
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**MRTs**	**Nuclear Medicine Technologists**	**Medical Physicists**
YT	0	0	0	0	0
NT	0	0	26	1	0
NU	0	0	0	0	0
Total	**2,034**	**221**	**12,255**	**1,781**	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRTs = Medical radiation technologists; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PE = Prince Edward Island; QC = Quebec; YT = Yukon.
* this represents a total for all of the jurisdictions

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies across Canada. Table 7 provides an overview of the availability of equipment required to diagnose AVN. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of MRI and SPECT/CT scanners is current to January 1, 2010.

Table 7: Diagnostic Imaging Equipment in Canada[7,43]			
	Nuclear Medicine Cameras	**MRI Scanners**	**SPECT/CT Scanners**
Number of devices	603[7]	218[43]	96[43]
Average number of hours of operation per week (2006-2007)[7]	40	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	YT, NT, NU	PE, YT, NT, NU

NT = Northwest Territories; NU = Nunavut; PE = Prince Edward Island; YT = Yukon.

Bone scanning

For bone scintigraphy, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions, the Yukon, the Northwest Territories, and Nunavut, do not have any nuclear medicine equipment.[7]

MRI

No MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[43] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario with a national average of 71 hours.[7] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[44]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of bone scanning and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 8), the cost of whole body bone scan with ^{99m}Tc-based radioisotopes is $344.016. MRI is a minimally more costly alternative.

Table 8: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[57]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
Bone scan				
J867	Blood flow and pool imaging	58.75	29.30	88.05
J851	Bone scintigraphy — single site	87.00	50.95	137.95
J819	Application of tomography (SPECT)	44.60	31.10	75.70
Maintenance fees — global budget		42.31		42.31
	TOTAL	**232.66**	**111.35**	**344.01**
MRI				
X471C	Multislice sequence, one extremity and/or one joint		66.10	66.10
X475C (×3)	Repeat (another plane, different pulse sequence; to a maximum of 3 repeats)		33.10 (×3) = 99.30	99.30
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		36.50		36.50
	TOTAL	336.50	165.40	**501.90**

MRI = magnetic resonance imaging; SPECT = single-photon emission computed tomography.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

^{99m}Tc = technetium-99m.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Database(s): EBM Reviews - ACP Journal Club 1991 to February 2011 EBM Reviews - Cochrane Central Register of Controlled Trials 1st Quarter 2011 EBM Reviews - Cochrane Database of Systematic Reviews 2005 to February 2011 EBM Reviews - Cochrane Methodology Register 1st Quarter 2011 EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2011 EBM Reviews - Health Technology Assessment 1st Quarter 2011 Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to March 11, 2011 **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	March 11, 2011
Alerts:	Monthly search updates began March 11, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

MULTI-DATABASE STRATEGY	
#	Searches
1	exp Osteonecrosis/
2	(osteonecros* or kienbock* disease* or kienboeck* disease or osteochondritis dissecans or bone infarction* or Perthes* disease).tw.
3	((avascular or aseptic or ischemic or ischaemic or femur head or femoral head or bone or bones) adj2 (necrosis or necroses)).tw.
4	(ONJ or AVN or SONK).ti,ab.
5	or/1-4
6	Technetium/ or exp Technetium Compounds/ or exp Organotechnetium Compounds/ or exp Radiopharmaceuticals/ or Radionuclide Imaging/ or Perfusion Imaging/
7	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.
8	radionuclide imaging.fs.
9	radioisotope*.mp.
10	((radionucl* or nuclear or radiotracer*) adj2 (imag* or scan* or test* or diagnos*)).ti,ab.
11	Tomography, Emission-Computed, Single-Photon/
12	(single-photon adj2 emission*).ti,ab.
13	(SPECT or scintigraph* or scintigram* or scintiphotograph*).ti,ab.
14	(medronate or methyl diphosphonate).ti,ab.
15	exp Joints/ri or exp "bone and bones"/ri
16	((bone or bones or joint or joints or MDP) adj2 (scan* or imag* or scintigraph*)).ti,ab.
17	or/6-16
18	5 and 17
19	((avascular necrosis or osteonecrosis or asceptic necrosis or ischemic) adj2 (scan* or imag* or scintigraph*)).tw.
20	18 or 19
21	remove duplicates from 20
22	limit 21 to english language [Limit not valid in ACP Journal Club,CCTR,CDSR,CLCMR,DARE; records were retained]
23	meta-analysis.pt.
24	meta-analysis/ or systematic review/ or meta-analysis as topic/ or exp technology assessment, biomedical/
25	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
26	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
27	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
28	(data synthes* or data extraction* or data abstraction*).ti,ab.
29	(handsearch* or hand search*).ti,ab.
30	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
31	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).ti,ab.
32	(meta regression* or metaregression* or mega regression*).ti,ab.
33	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
34	(medline or Cochrane or pubmed or medlars).ti,ab,hw.
35	(cochrane or health technology assessment or evidence report).jw.
36	(meta-analysis or systematic review).md.

MULTI-DATABASE STRATEGY	
37	or/23-36
38	22 and 37
39	exp "Sensitivity and Specificity"/
40	False Positive Reactions/
41	False Negative Reactions/
42	du.fs.
43	sensitivit*.tw.
44	(predictive adj4 value*).tw.
45	Comparative Study.pt.
46	(Validation Studies or Evaluation Studies).pt.
47	Randomized Controlled Trial.pt.
48	Controlled Clinical Trial.pt.
49	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
50	Multicenter Study.pt.
51	(random* or sham or placebo*).ti.
52	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
53	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
54	(control* adj3 (study or studies or trial*)).ti.
55	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
56	(allocated adj "to").ti.
57	Cohort Studies/
58	Longitudinal Studies/
59	Prospective Studies/
60	Follow-Up Studies/
61	Retrospective Studies/
62	Case-Control Studies/
63	Cross-Sectional Study/
64	(observational adj3 (study or studies or design or analysis or analyses)).ti.
65	cohort.ti.
66	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
67	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
68	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
69	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
70	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
71	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
72	(population adj3 (study or studies or analysis or analyses)).ti.
73	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
74	(distinguish* or differentiat* or enhancement or identif* or detect* or diagnos* or accura* or comparison*).tw.
75	or/39-74
76	75 not case reports.pt.
77	22 and 76
78	exp animals/
79	exp animal experimentation/

MULTI-DATABASE STRATEGY	
80	exp models animal/
81	exp animal experiment/
82	nonhuman/
83	exp vertebrate/
84	animal.po.
85	or/78-84
86	exp humans/
87	exp human experiment/
88	human.po.
89	or/86-88
90	85 not 89
91	77 not 90

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per Medline search, with appropriate syntax used.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	March 2011
Keywords:	Included terms for avascular necrosis and radionuclide imaging
Limits:	English language

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: ACR Appropriateness Criteria avascular necrosis of the hip[15]

The American College of Radiology (ACR) has updated its Relative Radiation Level categories and Rating Scale. The Rating Scale now includes categories (1, 2, 3 = Usually not appropriate; 4, 5, 6 = May be appropriate; 7, 8, 9 = Usually appropriate). See the original guideline document for details.

Clinical Condition: Avascular Necrosis (Osteonecrosis) of the Hip

Variant 1: Initial Study When AVN is Suspected Clinically			
Radiologic Procedure	**Rating**	**Comments**	**Relative Radiation Level**
X-ray pelvis	9	For initial evaluation in patients at risk for AVN who present with hip pain.	Low
X-ray hips	9	Frog-leg view is necessary to evaluate anterosuperior involvement of the femoral head.	Med
CT hips without contrast	1	Not useful for initial evaluation.	Med
^{99m}Tc bone scan with SPECT hips	1	Sensitive method for detecting AVN, but not indicated before radiographs.	Med
MRI hips with or without contrast	1	Most sensitive method for detecting AVN, but not indicated before radiographs.	None
Rating Scale: 1 = Least appropriate; 9 = Most appropriate.			

Variant 2: AVN with Femoral Head Collapse Detected by Radiographs of the Painful Hip: No Surgery Contemplated at This Time			
Radiologic Procedure	**Rating**	**Comments**	**Relative Radiation Level**
MRI hips without contrast	5	May be useful if knowledge of occult AVN in the opposite hip is needed.	None
^{99m}Tc bone scan with SPECT hips	1	May be useful if knowledge of occult AVN in the opposite hip is needed and MRI is not available.	Med
CT hips without contrast	1	Provides no more information than conventional radiographs. Shows subchondral fractures earlier, but not needed.	Med
Rating Scale: 1 = Least appropriate; 9 = Most appropriate.			

Variant 3: AVN with Femoral Head Collapse by Radiographs in the Painful Hip: Surgery Contemplated			
Radiologic Procedure	**Rating**	**Comments**	**Relative Radiation Level**
MRI hips without contrast	5	May be useful if knowledge of occult AVN in the opposite hip is needed or if surgical planning on either hip would be affected.	None
^{99m}Tc bone scan with SPECT hips	1	May be useful if knowledge of occult AVN in the opposite hip is needed and MRI is not	Med

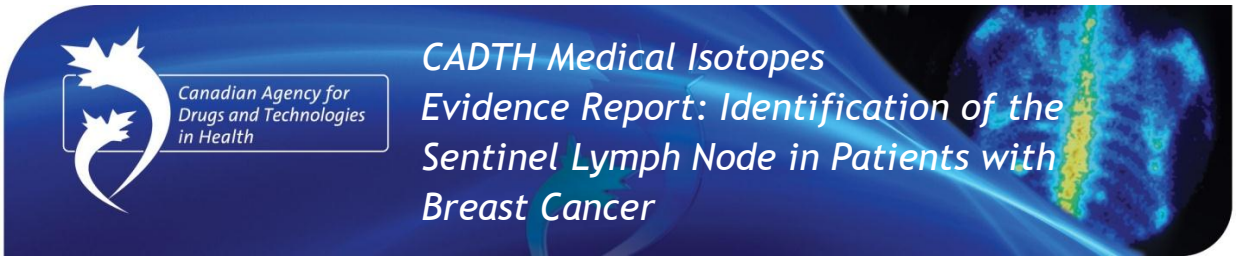
Variant 3: AVN with Femoral Head Collapse by Radiographs in the Painful Hip: Surgery Contemplated			
Radiologic Procedure	**Rating**	**Comments**	**Relative Radiation Level**
		available.	
CT hips without contrast	1	Provides no more information than conventional radiographs. May be useful if planning osteotomy by defining anatomic localization of the AVN and the extent of bone deformity.	Med
Rating Scale: 1 = Least appropriate; 9 = Most appropriate			

Variant 4: Radiograph Shows Mottled Femoral Head, Suspicious but Not Definite for AVN in the Painful Hip(s). Further Clinical Evaluation is Needed			
Radiologic Procedure	**Rating**	**Comments**	**Relative Radiation Level**
MRI hips without contrast	9	MRI provides definitive diagnosis when radiograph findings are equivocal.	None
^{99m}Tc bone scan with SPECT hips	6	If MRI is not available or is contraindicated.	Med
CT hips without contrast	6	If MRI is not available or is contraindicated. May show subchondral fracture not seen on MRI.	Med
Rating Scale: 1 = Least appropriate; 9 = Most appropriate.			

Variant 5: AVN Suspected Clinically But Radiographs Are Normal. Further Clinical Evaluation Needed.			
Radiologic Procedure	**Rating**	**Comments**	**Relative Radiation Level**
MRI hips without contrast	9	Most sensitive and specific method to establish or exclude AVN.	None
^{99m}Tc bone scan with SPECT hips	6	If MRI is not available or is contraindicated.	Med
CT hips without contrast	6	If MRI is not available or is contraindicated.	Med
Rating Scale: 1 = Least appropriate; 9 = Most appropriate			

AVN = avascular necrosis; CT = computer tomography; MRI = magnetic resonance imaging; SPECT = single photon emission computer tomography; ^{99m}Tc = Technetium-99m.

APPENDIX 2.16



INDICATION OVERVIEW

The sentinel node is the first lymph node that is affected when cancer spreads from a primary tumour to the lymph nodes. In breast cancer, the sentinel lymph node(s) (SLN) would generally be the lymph node that receives drainage from the breast. Once this node has been identified, it is biopsied (i.e., sampled [sentinel lymph node biopsy, or SLNB]). If this node does not contain cancer cells, it is unlikely that the cancer has spread.[1] If the SLN contains cancer cells, then an axillary lymph node dissection (ALND; dissection of many nodes throughout the axilla) or complete lymph node dissection (CLND) may be indicated.

Population: Patients with a diagnosis of breast cancer who are clinically node negative (clinical stage I and stage II).

Intervention: Technetium-99m–labelled sulphur colloid (^{99m}Tc-SC) or human albumin colloid (all radiopharmaceuticals are referred to in text as ^{99m}Tc) plus blue dye (isosulfan or methylene).

Identification of the SLN(s) is done during the surgery to remove the primary tumour of the breast. Prior to surgery, ^{99m}Tc is injected into the skin or parenchyma of the breast in the vicinity of the tumour or a subareolar location. The technique of injecting the radiolabelled agent and subsequent localization is known as lymphoscintigraphy and is typically performed on the day of surgery or the day prior to surgery to identify the location of the SLN or group of nodes and lymphatic channels. While in the operating suite, the patient is injected with blue dye and the breast is massaged to stimulate lymphatic flow. During the tumour removal surgery, a hand-held gamma counter is used to locate the SLN, which will have a high radioactivity count, and under visual inspection, the lymphatic channel and the SLN will be blue. The SLN is then biopsied and the sample is assessed to determine whether it contains cancer cells.

Comparators: For this report, the following diagnostic tests are considered as alternatives to ^{99m}Tc-labelled sulphur colloid or human albumin colloid with or without blue dye:

- *Blue dye alone (isosulfan or methylene)*
- *ALND*

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2: Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test

- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2010, Issue 11) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging, sentinel lymph node detection, and breast cancer.

Methodological search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials (RCTs), and non-randomized studies, including diagnostic accuracy studies. Where possible, retrieval was limited to the human population. No date limits were applied for systematic reviews. For primary studies, the retrieval was limited to documents published between January 1, 2006, and November 16, 2010. The search was also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

Seventy-four HTA/SR/MA articles were identified through the filtered search and 33 were subjected to full-text review. Three of the 33 were meta-analyses of the accuracy of identifying the SLN using ^{99m}Tc-based imaging. Two of these were retained,[2,3] with the third citation[4] reporting data from the two meta-analyses identified through the original searches. An additional meta-analysis was identified through the references of the retained meta-analyses.[5] Two systematic reviews[6,7] that compared the diagnostic accuracy of SLNB (the sentinel node was identified using ^{99m}Tc-based imaging) with ALND were included for comparison purposes, for the criterion of diagnostic accuracy. Seven articles identified through the HTA/SR/MA search reported information regarding the safety of the interventions, quality of life of patients undergoing breast cancer staging, and expertise required to perform SLNB.[8-14]

Seventeen primary studies relevant to the diagnostic accuracy of ^{99m}Tc in combination with blue dye were identified, one of which was an RCT[15] and 16 of which were non-randomized

studies.[16-31] One additional RCT was identified through the literature search,[32] but was a duplicate of the included RCT.[15]

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	It was estimated that there would be 23,200 new cases (all stages) of breast cancer in 2010; incidence rate: 102/100,000 (0.1%). Based on registry data, 81% of women diagnosed with breast cancer had confirmed stage I, stage II, or unstaged disease and would have been candidates for imaging to identify the SLN.[33] Based on these data, the size of the affected population is estimated to be more than 1 in 10,000 (0.01%) and less than or equal to 1 in 1,000 (0.1%).
2	**Timeliness and urgency of test results in planning patient management**	Identification of the SLN for staging of breast cancer occurs at the time of tumour removal surgery. If the SLN is not identified by either ^{99m}Tc or blue dye, some women may undergo an ALND at the time of the tumour removal surgery. The test needs to be conducted at the time of surgery, and obtaining the test results in the appropriate timely manner for the underlying condition has significant impact on the management of the condition.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	If ^{99m}Tc is not available, the surgeon has the option of using blue dye alone, and if he or she does not feel comfortable using dye alone, an ALND may be performed. Diagnostic imaging test results have no impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	If ^{99m}Tc is not available, the surgeon has the option of using blue dye alone, and if he or she does not feel comfortable using dye alone, an ALND can be performed. An ALND is associated with higher morbidity (increased pain and swelling in the arm, and limitations to arm function) than selective removal of the sentinel node(s) via SLNB. If the alternative to ^{99m}Tc-based imaging is ALND, the diagnostic imaging test has a significant impact on morbidity or quality of life. If the alternative to ^{99m}Tc-based imaging is blue dye alone, the diagnostic imaging test has no impact on morbidity or quality of life.

Domain 2: Criteria Comparing a ^{99m}Tc-based Test with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	*^{99m}Tc-based imaging with blue dye* Patients may have concerns regarding the injection and the radiation exposure. Expert opinion states that no patient has refused the test based on the safety profile of ^{99m}Tc or blue dye; however, some patients do not like the sulphur colloid injections, due to a stinging sensation during the injection. *ALND* Patients may have concerns regarding post-operative complications. *Blue dye alone* Patients may have concerns regarding the injection. Patients are not exposed to radiation with blue dye alone. ^{99m}Tc-based imaging with blue dye is: • significantly more acceptable to patients than ALND • minimally less acceptable to patients than blue dye alone.
7	**Relative diagnostic accuracy of the test**	Overall, the identification rate with the combination of ^{99m}Tc-based radiopharmaceutical and blue dye ranged from 95% to 100% across the included studies. In all studies in which ^{99m}Tc-based radiopharmaceutical plus blue dye was compared with blue dye alone, the identification rate of the SLN was higher with the combination. A summary of the studies reporting SLN identification rates using ^{99m}Tc-based imaging methods alone or in combination with blue dye versus identification using blue dye alone are summarized in the table below.

Domain 2: Criteria Comparing a ^{99m}Tc-based Test with an Alternative or Comparing Between Clinical Uses

Criterion		Synthesized Information				
		Study	**^{99m}Tc Agent**	**SLN Identification Rate**		
				^{99m}Tc	**^{99m}Tc + BD**	**BD**
		Varghese et al. 2008[15]	nanocolloid	NP	98.7%	96.5%
		Hayashida et al. 2010[16]	tin colloid	94.7%	97.7%	79.6%
		Usmani et al. 2010[17]	nanocolloid	96%	98%	87%
		Yalcin et al. 2010[18]	HIG, nanocolloid	92% 96%	NP	96% 100%
		Hojo et al. 2010[19]	phytate	100%	NP	92.9%
		Dixon et al. 2009[20]	albumin nanocolloid	NP	98.8%	NP
		Koukouraki et al. 2009[22]	nanocolloid	NP	99.3%	95.3%
		Mathelin et al. 2009[21]	colloidal rhenium sulphur	91%	NP	99%
		Noguchi et al. 2009[23]	phytate	97%	99.5%	98%
		Kargozaran et al. 2007[24]	sulphur colloid	97.6%	98.4%	92.7%
		Argon et al. 2006[25]	sulphur tin	90%	NP	88%
		D'Eredita et al. 2006[26]	human albumin colloid	NP	95%	94.6%
		Goyal et al. 2006[27]	albumin colloid	85.6%	96.0%	85.6%

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing a ^{99m}Tc-based Test with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>Kesmodel et al. 2006[28]</td><td>sulphur colloid</td><td>97%
98%</td><td>NP</td><td>96%
88%</td></tr>
<tr><td>Takei et al. 2006a[30]</td><td>HSA
phytate</td><td>89.5%
95.6%</td><td>97%
99.6%</td><td>94.7%
97.1%</td></tr>
</table>
BD = blue dye; HIG = human polyclonal immunoglobulin; HSA = human serum albumin; NP = not performed; ^{99m}Tc = technetium-99m.

Assuming competency using blue dye alone, the diagnostic accuracy of the ^{99m}Tc-based test is:
• similar to ALND
• minimally better than blue dye alone.</td></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>
^{99m}Tc-based imaging with blue dye

Identification of the SLN can involve isosulfan blue dye or methylene blue dye. Isosulfan blue dye is associated with allergic reactions, and methylene blue dye is known to result in skin reactions. There is a known contraindication of selective serotonin reuptake inhibitors and methylene blue dye. Both dyes can interfere with pulse oximetry readings.[34]

Patients receiving ^{99m}Tc-based imaging are exposed to radiation. Rare urticarial skin reactions have been reported with ^{99m}Tc-labelled albumin colloid.

ALND
The risks associated with ALND include acute hematoma, perioperative risks, extra time under anesthesia, and a longer length of stay in hospital. Longer hospitalization increases the risk of hospital-based infections (MIIMAC expert opinion).

Blue dye alone
Risks would include only those related to administration of the dye.

Overall, ^{99m}Tc-based imaging with blue dye:
• is minimally safer than ALND
• has a safety profile similar to that of blue dye alone.
</td></tr>
</table>

Domain 2: Criteria Comparing a ^{99m}Tc-based Test with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
9	**Relative availability of personnel with expertise and experience required for the test**	*^{99m}Tc-based imaging with or without blue dye* From the literature, it appears that there is a similar learning curve for proper identification of the SLN for ^{99m}Tc-based identification and using blue dye alone; however, expert opinion suggests that some surgeons may not feel comfortable performing SLN identification using blue dye alone. Competency is gained through increasing the number of procedures performed, which in turn lowers the false-negative rate. Tests may have to be done in tertiary care centres where the surgeon has the opportunity to become proficient with the identification of the SLN because there is likely to be a larger number of procedures performed. *ALND* Most general surgeons would be able to perform ALND. Assuming the necessary equipment is available, if ^{99m}Tc-based imaging using blue dye is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using ALND • 25% to 74% of the procedures can be performed in a timely manner using blue dye alone.
10	**Accessibility of alternative tests (equipment and wait times)**	Expert opinion states that blue dye is readily available and there have been no known shortages. ALND requires surgical supplies that would be readily available in hospitals. Assuming the necessary expertise is available, if ^{99m}Tc-based imaging using blue dye is not available, it is estimated that: • more than 95% of the procedures can be performed in a timely manner using ALND • more than 95% of the procedures can be performed in a timely manner using blue dye alone.

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing a ^{99m}Tc-based Test with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of SLNB with ^{99m}Tc-based radioisotopes is $791.27. ALNB is a minimally more costly alternative. SLNB with blue dye only is minimally less costly than SLNB with ^{99m}Tc-based radioisotopes and blue dye.

<table>
<tr><th colspan="3">Relative Costs</th></tr>
<tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr>
<tr><td>SLNB</td><td>791.27</td><td>Reference</td></tr>
<tr><td>SLNB (blue dye alone)</td><td>625.97</td><td>-165.30</td></tr>
<tr><td>ALND</td><td>938.66</td><td>+147.39</td></tr>
</table>
</td></tr>
</table>

ALND = axillary lymph node dissection; BD = blue dye; HIG = human polyclonal immunoglobulin; HSA = human serum albumin; NP = not performed; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; ^{99m}Tc = technetium-99m.

CRITERION 1: Size of affected population (link to definition)

Table 2 reports the stages of breast cancer.

Table 2: Stages of Breast Cancer[35]

Stage	Characteristics of Stage
0	Both DCIS, where abnormal cells are in the lining of a milk duct and have not spread outside the duct; and LCIS, where the abnormal cells are in the lining of the lobule
I	Tumour is 2 cm or smaller and has not spread outside the breast
II	Tumour is 2 to 5 cm or the cancer has spread to the lymph nodes, or both
III	The cancer has spread to the lymph nodes and may have spread to nearby tissues (muscle or skin)
IV	Cancer has spread to distant parts of the body

DCIS = ductal carcinoma in situ; LCIS = lobular carcinoma in situ.

Based on registry information using data current to 2008 from Manitoba, 81% of women diagnosed with breast cancer had confirmed stage I, stage II, or unstaged disease and would have been candidates for imaging to identify the SLN.[33]

In patients with clinical stage 0 and I, it has been shown that axillary nodes failed to contain metastases in more than 75% of cases.[36]

Based on the guidelines from the American Society of Clinical Oncology, regarding SLNB in early-stage breast cancer, the population recommended to receive SLNB are those patients with clinical stage I or stage II disease. The level of evidence for this recommendation is "Good."[37] The Canadian Cancer Society has reported the estimated incidence rate for 2010 to be 102/100,000 population.[38] Therefore, based on the assumption from the Canadian study,[39] 87.8% of women diagnosed with breast cancer have stage I, stage II, or unstaged (not enough information to indicate a stage)[40] disease and are candidates for imaging to identify the SLN (89/100,000 [approximately 0.09%]).

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CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Identification of the SLN for staging of breast cancer occurs at the same time as the tumour removal surgery. If SLN is not identified by this time, women will likely undergo an ALND at the time of the tumour removal surgery.[14]

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CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

There is no impact on mortality of not performing the test. Patients not undergoing biopsy of the SLN (SLNB) can receive ALND.

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CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

The assumption is that most patients who do not receive SLNB will undergo ALND. ALND is the most common cause of secondary lymphedema, with 7% to 34% of women experiencing arm swelling.[2]

The overall complication rate of SLNB is statistically significantly lower at 3% compared with 35% for ALND (P = 0.001).[2] Complications of ALND reported include wound infections, lymphedema, limited arm motion and strength, pain and discomfort, numbness and paresthesia, tightness, stiffness, and tingling.

Kell et al.[9] reported a statistically significant reduction in risk of arm swelling at six months with SLNB compared with full ALND (odds ratio [OR] = 0.30; 95% confidence interval [CI], 0.14 to 0.66; P = 0.0028).[9]

One prospective cohort study[41] followed women with clinical stage I and II tumours who underwent SLNB, or SLNB and CLND (SLNB + CLND), or ALND. As reported in Table 3, patients undergoing SLNB had the fewest number of lymph nodes dissected.[41]

Table 3: Number of Patients Undergoing Dissection Stratified by Lymph Node Frequency Group and Technique.[41]

Number of Dissected Lymph Nodes	Staging Technique		
	SLNB (n = 51)	SLNB + CLND (n = 56)	ALND (n = 65)
Fewer than 3	48	0	0
3 to 10	1	20	25
More than 10	0	32	37
Missing	2	4	3

ALND = axillary lymph node dissection; CLND = complete axillary lymph node dissection; SLNB = sentinel lymph node biopsy.

Quantitative measurements of the shoulder and arm function and the level of lymphedema were measured over a 24-month period beginning with a preoperative baseline measurement of both arms. The SLNB procedure group had significantly fewer arm functional limitations compared with SLNB + CLND for two measures (P < 0.02) and for three measures compared with ALND (P < 0.01). There was a significant increase in arm volume in the SLNB + CLND (P = 0.041) and the ALND (P < 0.001) groups, but not in the SLNB group from baseline, and the arm volume increase was significantly smaller in the SLNB compared with the ALND group (P = 0.001).

Two studies[42,43] measured quality of life using the European Organisation for Research and Treatment of Cancer (EORTC) quality of life questionnaires, QLQ-C30 and QLQ-BR23. Both studies were prospective cohort studies comparing patients who underwent SLNB only with those who underwent ALND. Dabakuyo et al.[42] also included a third group who had SLNB followed by ALND. Patients in both studies were assessed at 12 months after surgery.

Dabakuyo et al.[42] followed a cohort of women (n = 518) and reported that the SLNB group had a significantly better global health status and better arm symptom score (pain, swelling, and mobility) at 12 months than the other two groups (ALND or SLNB + ALND; P < 0.0001). There were a large number of missing data points in all three groups across the 12 months. After

modelling the missing data, the arm functioning quality of life score was statistically significantly better for the SLNB group compared with the SLNB + ALND: P = 0.0013. There was no difference in the scores between the ALND and the SLNB + ALND groups.

Peintinger et al.[43] confirmed that SLNB is associated with less morbidity of the arm and shoulder than ALND (n = 56). Specifically, they found that differences in post-discharge pain, measured by the EORTC QLQ-C30, were statistically significant (P < 0.05) and favoured SLNB. Pain levels measured nine to 12 months post-discharge, using a visual analogue scale, were also statistically significant (P < 0.05) and favoured SLNB.

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CRITERION 5: Relative impact on health disparities (link to definition)

Male breast cancer is rare, accounting for approximately 1% of all cases of breast cancer.[44]

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CRITERION 6: Relative acceptability of the test to patients (link to definition)

No literature was identified in the literature searches regarding the acceptability to patients of imaging tests to identify the SLN. Expert opinion states that no patient has refused the ^{99m}Tc-based test based on the safety profile. Expert opinion suggests that patients do not like the sulphur colloid because it stings during the injection and for the first few minutes after the injection (MIIMAC expert opinion).
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CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Systematic reviews

Two systematic reviews were included in this review for comparison purposes. Both reviews included studies that compared the diagnostic accuracy of SLNB (the sentinel node was identified using ^{99m}Tc-based imaging) with ALND. Primary studies for this comparison were not reviewed for this report.

SLNB versus ALND
Spillane et al.[6] performed a systematic review to evaluate the accuracy of SLNB in multifocal, multicentric, and larger breast cancers compared with ALND (Table 4, Appendix 4). There did not appear to be any restriction on study design; however, the design of the final studies selected for inclusion was not reported. The review included a total of 26 studies, 23 of which compared SLNB with ALND, with radioisotope-based imaging to locate the SLNs. The remaining studies used blue dye alone in locating the SLNs. Diagnostic accuracy was presented according to tumour type (multifocal, multicentric, or large) and was not pooled across studies. The observed diagnostic accuracy, false-negative rates (FNRs), sensitivities, and negative predictive values were highly variable across studies, and the authors concluded that the observed rates were similar to those observed in patients with small, unifocal breast cancers (Table 6, Appendix 4). This systematic review had a number of limitations, as outlined in Table 6, Appendix 4, one of which was a failure to report details of the radiopharmaceutical used in the identification of the SLNs. Rather, the radiopharmaceutical used was simply described as “radiocolloid.”

The National Breast and Ovarian Cancer Centre[7] conducted a systematic review of the literature, with the objective of comparing SLNB with standard ALND in early breast cancer (Table 4, Appendix 4). Four RCTs were included that contained information on diagnostic accuracy of SLNB compared with ALND when ^{99m}Tc-based radiopharmaceuticals were used to locate the SLNs. Data pertaining to diagnostic accuracy were not pooled across studies. FNRs with SLNB ranged from 8.2% to 16.7%, while sensitivity ranged from 83.3% to 92% and the negative predictive values ranged from 92.3% to 97% (Table 6, Appendix 4). The review authors concluded that false negatives can occur at a similar rate with both SLNB and ALND. This systematic review appeared to be methodologically rigorous, but the failure to include non-randomized studies could be one potential limitation of the review.

^{99m}Tc-based imaging (with or without blue dye) versus blue dye alone

Our review of the literature identified four systematic reviews and 17 primary studies of the diagnostic accuracy of ^{99m}Tc-based radiopharmaceutical plus isosulfan blue dye in the detection of SLN.

Primary studies

SLNB ± blue dye versus blue dye alone

The study objectives and details of study design are summarized in Table 5, Appendix 4. The number of patients included in the studies ranged from 50[18] to 842.[27] Five studies were conducted in Japan,[16,19,23,30,31] three in the United Kingdom,[15,20,27] two in the United States,[24,28] two in Turkey,[18,25] and one in each of Italy,[26] Austria,[29] France,[21] Kuwait,[17] and Greece.[22] No studies were conducted in Canada. Nine of the non-randomized studies were prospective[16-21,23,27,29] and two were retrospective.[28,30] It was unclear if the remaining five studies were prospective or retrospective.[22,24-26,31]

Additional details of exclusion criteria and patient characteristics can be found in Table 8, Appendix 5. Seven studies excluded patients based upon previous surgery, radiation, or chemotherapy.[15,17,18,22,25-27] However, there were seven studies in which no exclusion criteria were reported.[16,19,23,28-31] In these studies, it was unclear whether all patients who underwent treatment at the study site during the time frame of the study were included, or whether these details were not reported.

Details of the intervention and comparator (radioisotope-based imaging and blue dye) can be found in Appendix 6, including the specific radioisotope or dye that was used, the dosage, administration technique, and timing of administration relative to surgery. ^{99m}Tc-sulphur colloid was used in two studies,[24,28] ^{99m}Tc-albumin in four studies,[20,26,27,30] ^{99m}Tc-phytate in four studies,[19,23,30,31] ^{99m}Tc-tin colloid in two studies,[16,25] ^{99m}Tc-nanocolloid in five studies,[15,17,18,22,29] and ^{99m}Tc-rhenium in one study.[21] The blue dyes that were used differed across studies, with patent blue dye,[19,20,23,27,29-31] isosulfan blue dye,[16-18,22,25,28] and methylene blue dye[15,21,26] being used most frequently.

Study outcomes

The main study outcomes were the proportion of patients in whom one or more SLNs were successfully mapped (the identification rate) and measures of agreement or concordance between the blue dye and the ^{99m}Tc-based radiopharmaceutical (Table 7, Appendix 4).

The identification rate with the combination of ^{99m}Tc-based radiopharmaceutical and blue dye ranged from 95%[26] to100% (Table 7, Appendix 4) across the included studies.[22] In all studies in which ^{99m}Tc-based radiopharmaceutical was compared with blue dye alone, the identification

rate was higher with the combination, indicating that SLN mapping was less successful with blue dye alone.[15-17,22-24,26,27,30,31] In five studies that reported a comparison between ^{99m}Tc-based radiopharmaceutical alone and blue dye alone, the identification rate was higher with the ^{99m}Tc-based radiopharmaceutical.[16,17,19,28,30] Two studies reported higher identification rates with blue dye alone than with ^{99m}Tc-based radiopharmaceutical alone[18,23] and one study reported the same identification rate.[27]

In all studies that reported on agreement between ^{99m}Tc-based radiopharmaceutical and blue dye, there was some discordance in identification, with some SLNs being stained (blue) but not radioactive (hot), or radioactive but not stained (Table 7, Appendix 4).

Limitations
The limitations of the included studies are outlined in Table 7, Appendix 4. Generally, the limitations were similar across studies and related to factors that could potentially affect the generalizability of the results. For example, details on the experience of the individuals performing the mapping were not reported, so the identification rates could not be interpreted relative to the degree of experience. As well, the effects of improving technique as experience is gained were not captured in the included studies, which were often conducted over a number of years. Further, details on previous treatments, adjuvant chemotherapy in particular, were often not reported. Thus, it was not clear for a number of studies to what population (with respect to previous treatment status) the study results would be generalizable.

A number of different ^{99m}Tc-based radiopharmaceuticals were used for SLN mapping in the included studies. If the ^{99m}Tc-based radiopharmaceuticals used in some studies are not available or used in Canada, the results might not be generalizable to the Canadian population. Identification rates could potentially differ between the different ^{99m}Tc-based radiopharmaceuticals. While the identification rate of SLNs with ^{99m}Tc-based radiopharmaceutical compared with blue dye was reported in most studies, few studies reported an overall concordance rate. In some studies, comparison between ^{99m}Tc-based radiopharmaceutical and blue dye was not the primary objective of the study, so conclusions specific to this comparison were not made.

In a limited number of the included studies, patients who had stage III or IV disease were included.

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CRITERION 8: Relative risks associated with the test (link to definition)

SLNB with ^{99m}Tc-labelled colloid + blue dye
Rare urticarial skin reactions have also been reported with ^{99m}Tc-labelled albumin colloid.[45] Patients may experience reactions to the blue dye (isosulfan and methylene) that may include allergic reactions and skin reactions.[2,34] Anaphylactic reactions to isosulfan blue dye have been reported to occur in approximately 1% of patients.[34,46] Both dyes can interfere with pulse oximetry readings.[34]

In addition to the contraindications and adverse reactions noted for blue dye, a recent Health Canada notice[47] reports an association of serotonin toxicity with methylene blue injectable in combination with serotonin reuptake inhibitors. Several of the reported cases required admission to the intensive care unit.

SLNB with blue dye only
If the lymphatic system or the SLN is deep, localization with blue dye may require a large incision, causing a disturbance to the lymphatic channels, which in turn may impair visualization of the node.[48] The ^{99m}Tc technique may be more precise and has less surgical morbidity compared with the blue dye.[5] The incidence rate of allergic and anaphylactic reactions to isosulfan blue in SLNB ranged from 1% to 3%.[49]

ALND
ALND is a more invasive surgical procedure than SLNB and requires general anesthesia.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

A close correlation has been reported between the number of procedures performed and the localization rate for the technique, ranging from 71% after a surgeon has performed fewer than 40 procedures, to 98% after performing hundreds of procedures.[50] Three groups of surgeons have been identified from evaluating learning curves based on surgeon-specific and institution-specific surgical volume analyses. Those identified perform: 1) more than six procedures a month, with a 4% failure-to-identify rate; 2) two to six per month, with a failure rate of 12%; and 3) fewer than two per month, with a failure rate of 15% to 18%.[11] Tests may have to be done in tertiary care centres where the surgeon has the capability to become proficient in identifying the SLN. The study published in 2000[11] reported that the average general surgeon in the United States cares for five patients with breast cancer a year and likely would not be able to achieve proficiency.[11] While the number of surgeons in Canada is reduced compared with the United States, so too is the number of cases of breast cancer.

One multi-centre trial reported an improvement in the FNR from 5.8% to 4.3% (95% confidence intervals not reported) after the surgeons had completed 30 procedures.[3] A Canadian review reported that appropriate surgeon performance is achieved with 50 or fewer biopsies, and generally with fewer than 20 biopsies.[4] Another study reported that surgeon accrual of 50 or fewer patients was associated with an increased likelihood of failure to identify the SLN ($P \leq 0.001$).[36] The FNR has been reported to have risen slightly from 3.2% to 4.3% from 1998 to 2003 in Australia.[2] This may, in fact, be due to improvements in pathology methods used to identify small metastases (macro sectioning of many nodes in early trials versus micro sectioning of very few nodes in later trials) than in the actual surgical technique.[48]

Expert opinion suggests that some surgeons may not feel comfortable performing SLN identification using blue dye alone.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

No literature was identified through the searches on accessibility of blue dye in Canada.

Expert opinion states that it is readily available and there have been no known shortages. Blue dye does not break down, but if not stored correctly, it is subject to bacterial growth (MIIMAC expert opinion).

ALND
Most general surgeons in Canada would be able to perform ALND.

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of SLNB and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., positron emission tomography scan, computed tomography scan, magnetic resonance imaging scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 4), the cost of SLNB with ^{99m}Tc-based radioisotopes is $791.27. ALNB is a minimally more costly alternative. SLNB with blue dye only is minimally less costly than SLNB with ^{99m}Tc-based radioisotopes and blue dye.

Table 4: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[51]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
SLNB				
J861	Radionuclide lymphangiogram	115.10	62.20	165.30
Z427	Sentinel node biopsy, per draining basin		330.45 (Surg) 72.24 (Asst) 120.08 (Anes)	522.77
L865	Surgical pathology, level 5 Gross and microscopic examination of the following specimens: lymph nodes (regional resection; sentinel)		103.20	103.20
	TOTAL		791.27	**791.27**
SLNB (with blue dye alone)				
Z427	Sentinel node biopsy, per draining basin		330.45 (Surg) 72.24 (Asst) 120.08 (Anes)	522.77
L865	Surgical pathology, level 5 Gross and microscopic examination of the		103.20	103.20

Table 4: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[51]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
	following specimens: lymph nodes (regional resection; sentinel)			
	TOTAL		625.97	**625.97**
	ALND			
R111	Partial mastectomy or wedge resection for treatment of breast disease, with or without biopsy; e.g., carcinoma or extensive fibrocystic disease		269.40 (Surg) 72.24 (Asst) 105.07 (Anes)	446.71
E546	With axillary node dissection up to the level of the axillary vein		388.75	388.75
L865	Surgical pathology, level 5 Gross and microscopic examination of the following specimens: lymph nodes (regional resection; sentinel)		103.20	103.20
	TOTAL		938.66	**938.66**

ALND = axillary lymph node dissection; anes = anesthetic; asst. = assistant; prof. = professional; SLNB = sentinel lymph node biopsy; surg = surgical; tech. = technical.

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APPENDICES

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the technetium-99m (^{99m}Tc)-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
	clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE <1950 to November Week 3 2010> Ovid MEDLINE In-Process & Other Non-Indexed Citations <November 16, 2010>
Date of Search:	November 17, 2010
Alerts:	Monthly search updates began November 17, 2010 and ran until October 2011
Study Types:	health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, diagnostic accuracy studies, and economic studies
Limits:	Publication years 2006-November 16, 2010 for primary studies; no date limits for systematic reviews English language Humans, where possible

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.tw	Text Word; includes title and abstract
.pt	Publication type
.nm	Name of Substance Word
.mp	Keyword search; includes protocol supplementary concept, rare disease supplementary concept, title, original title, abstract, name of substance word, subject heading word, unique identifier
/ri	Radionuclide imaging

OVID MEDLINE Strategy	
#	**Searches**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	(Technetium* or Tc-99 or Tc99 or Tc-99m or Tc99m or 99mTc or 99m-Tc).tw,nm.

OVID MEDLINE Strategy	
6	Molybdenum/
7	(molybdenum-99 or Mo-99 or moly cow or molybdenum cow).tw,nm.
8	Radionuclide Imaging/
9	Radioimmunodetection/
10	exp *Breast Neoplasms/ri
11	(or/1-10) and (lymph* or (sentinel adj2 node?)).mp.
12	Lymph Nodes/ri
13	Lymphatic System/ri
14	Lymphatic Metastasis/ri
15	Sentinel Lymph Node Biopsy/
16	((scintigraph* or scintigram* or scintiphotograph* or gamma camera? or gamma imag* or nuclear camera? or scinti-camera? or scintillation camera? or immunoscintigraph* or radioimmunoimag* or radioimmunoscintigraph*) and (lymph* or (sentinel adj2 node?))).mp.
17	(lymphoscintigraph* or lympho-scintigraph* or lymphatic mapping).mp.
18	(sentinel adj2 node? adj3 (detect* or identif* or map* or locali*)).mp.
19	SNOLL.ti,ab.
20	or/11-19
21	exp Breast Neoplasms/
22	((breast or mammary) adj2 (cancer* or carcinoma? or neoplasm? or tumor? or tumour? or malignanc*)).tw.
23	or/21-22
24	20 and 23
25	Meta-Analysis.pt.
26	Meta-Analysis.sh. or exp Technology Assessment, Biomedical/
27	((systematic* adj (literature review* or review* or overview*)) or (methodologic* adj (literature review* or review* or overview*))).tw.
28	((quantitative adj (review* or overview* or synthes*)) or (research adj (integration* or overview*))).tw.
29	((integrative adj2 (review* or overview*)) or (collaborative adj (review* or overview*)) or pool* analy*).tw.
30	(data synthes* or data extraction* or data abstraction*).tw.
31	(handsearch* or hand search*).tw.
32	(meta analy* or metaanaly* or met analy* or metanaly* or health technology assessment* or HTA or HTAs or biomedical technology assessment* or bio-medical technology assessment*).tw.
33	(meta regression* or metaregression* or mega regression*).tw.
34	or/25-33

OVID MEDLINE Strategy	
35	exp "Sensitivity and Specificity"/
36	False Positive Reactions/
37	False Negative Reactions/
38	du.fs.
39	sensitivit*.tw.
40	(predictive adj4 value*).tw.
41	distinguish*.tw.
42	differentiat*.tw.
43	enhancement.tw.
44	identif*.tw.
45	detect*.tw.
46	diagnos*.tw.
47	accura*.tw.
48	comparison*.tw.
49	Comparative Study.pt.
50	(Validation Studies or Evaluation Studies).pt.
51	Randomized Controlled Trial.pt.
52	Controlled Clinical Trial.pt.
53	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
54	Multicenter Study.pt.
55	(random* or sham or placebo*).ti.
56	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
57	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
58	(control* adj3 (study or studies or trial*)).ti.
59	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
60	(allocated adj "to").ti.
61	Cohort Studies/
62	Longitudinal Studies/
63	Prospective Studies/
64	Follow-Up Studies/
65	Retrospective Studies/
66	Case-Control Studies/
67	Cross-Sectional Study/
68	(observational adj3 (study or studies or design or analysis or analyses)).ti.
69	cohort.ti.

OVID MEDLINE Strategy	
70	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
71	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
72	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
73	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
74	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
75	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
76	(population adj3 (study or studies or analysis or analyses)).ti.
77	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
78	or/35-77
79	Case Reports.pt.
80	78 not 79
81	*Economics/
82	exp "Costs and Cost Analysis"/
83	"Quality of Life"/ or "Value of Life"/ or Quality-Adjusted Life Years/
84	exp Models, Economic/ or Markov Chains/ or Monte Carlo Method/ or Decision Trees/
85	(economic* or cost? or costing or costly or costed or cost-effective* or costeffective* or cost-utili* or costutili* or price? or pricing?).tw.
86	(sensitivity analysis or sensitivity analyses).tw.
87	(pharmacoeconomic? or (pharmaco adj economic?) or budget* or expenditure*).tw.
88	(value adj1 (money or monetary)).tw.
89	(fee or fees or "quality of life" or qol* or hrqol*).tw.
90	("quality adjusted life year*" or qaly* or cba or cea or cua or utilit* or markov* or monte carlo).tw.
91	or/81-90
92	24 and 34
93	limit 92 to english language
94	24 and 80
95	limit 94 to (english language and humans and yr="2006 -Current")
96	24 and 91
97	limit 96 to (english language and yr="2006 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane	Same MeSH, keywords, and date limits used as per MEDLINE search,

Library (Issue 11, 2010)	excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	November 2010
Keywords:	Included terms for sentinel lymph node detection and breast cancer.
Limits:	Publication years 2006 to November 2010

The following sections of the CADTH grey literature checklist, “Grey matters: a practical search tool for evidence-based medicine” (http://www.cadth.ca/en/resources/grey-matters) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Definitions

Anaphylactic shock: A widespread and very serious allergic reaction. Symptoms include dizziness, loss of consciousness, laboured breathing, swelling of the tongue and breathing tubes, blueness of the skin, low blood pressure, heart failure, and death.

Axillary lymph node: A lymph node found in any of the axilla regions: stage I — nodes that are lateral and inferior to the pectoralis minor muscle; stage II — nodes under the pectoralis minor muscle; stage III — nodes under and deep to the pectoralis minor muscle.

Bradycardia: Resting heart rate below 60 beats per minute.

Hypoxia: Deficiency in the amount of oxygen being delivered to the body.

Necrosis: Premature death of cells or tissue.

Sentinel lymph node: First node on the direct lymphatic pathway draining from a tumour.

Subareolar: Below the coloured area surrounding the nipple of the breast.

Appendix 4: Characteristics of Included Studies

Systematic Reviews

Table 4: Objective and Details of Study Design of the Included Systematic Reviews

Report	Objective	Study Eligibility	Number of Included Studies	Search Time frame	Comments on Quality
Spillane et al. 2011[6]	To systematically review the evidence of accuracy of SLNB in multifocal, multicentric, and larger breast cancers	**Inclusion:** **Population:** Patients with clinically node-negative invasive breast cancer and multifocal or multicentric tumours or tumours with diameters 30 mm or greater **Intervention:** SLNB **Comparator:** ALND **Outcome:** Sensitivity, specificity, and either success rate of SLN identification or SLN positivity rate. **Design:** No restrictions on study design were reported **Exclusion:** Studies in which all patients did not receive SLNB and ALND Studies reporting fewer than 20 cases Studies that did not give any information on accuracy Studies of SLNB after neoadjuvant chemotherapy.	26 studies in total, 23 of which used SLN mapping techniques relevant to the research question for this report Radiocolloid alone: Multicentric tumours only — 0 studies Multifocal tumours only — 1 study Multicentric or multifocal tumours together — 2 studies Large tumours — 0 studies Radiocolloid with blue dye Multicentric tumours only — 5 studies Multifocal tumours only — 3 studies Multicentric or multifocal tumours together — 6 studies Large tumours — 8 studies	1950 to April 2010	In the Methods section of the report, it was stated that the quality of included studies was assessed, but methodology was not described and the results of the quality assessment were not reported.

Table 4: Objective and Details of Study Design of the Included Systematic Reviews					
Report	**Objective**	**Study Eligibility**	**Number of Included Studies**	**Search Time frame**	**Comments on Quality**
National Breast and Ovarian Cancer Centre 2008[7]	To compare SLNB with standard ALND in early breast cancer	**Inclusion:** **Population:** Patients with clinically node-negative, operable invasive breast cancer **Intervention:** SLNB with SLN identification using radioactive isotope and/or blue dye **Comparator:** ALND **Outcome:*** Overall survival, disease-free survival, morbidity, quality of life, adverse events **Study Design: RCTs** **Exclusion:** Studies that were not original clinical studies Studies that were not phase III RCTs Studies conducted in a populations other than patients with early breast cancer Non-English language	6 studies in total, 4 of which reported diagnostic accuracy of SLNB compared with ALND **SLN identification technique**: Radiopharmaceutical alone — 2 studies Radiopharmaceutical with dye — 2 studies **Radiopharmaceutical used:** ^{99m}Tc-albumin nanocolloid — 1 study ^{9m}Tc-albumin colloid — 1 study ^{99m}Tc-sulphur colloid — 2 studies	January 2000 to July 2007	Specific aspects of the studies according to the NSW Health Method for Evaluating Research Guideline Evidence (MERGE) tool. Results of the quality assessment were briefly reported. Two studies were published in abstract form only, which impeded the ability to assess quality to some extent, according to the authors. Allocation concealment was often not reported. Baseline patient characteristics were described as well balanced between study arms. The review authors stated that it was unlikely that the

Table 4: Objective and Details of Study Design of the Included Systematic Reviews					
Report	**Objective**	**Study Eligibility**	**Number of Included Studies**	**Search Time frame**	**Comments on Quality**
					included RCTs were significantly influenced by bias or confounding as they were well-designed RCTs.

ALND = axillary lymph node dissection; mm = millimeter; RCT = randomized controlled trial; SLNB = Sentinel lymph node biopsy; SLN = sentinel lymph node; ^{99m}Tc = technetium-99m.
* Included studies in which SLNB was followed by ALND also reported outcomes of diagnostic accuracy.

Primary Studies

Table 5: Objective and Details of Study Design of the Included Primary Studies				
Study	**Objective**	**Population**	**Study Design**	**Location**
Varghese et al. 2008[15]	To evaluate the suitability of methylene blue dye as a dye for SLN biopsy	Number of patients: 329 Cancer type: Early breast cancer	Described as a retrospective analysis of data from an RCT comparing methylene blue dye (n = 173) with methylene blue dye combined with ^{99m}Tc-based radiopharmaceuticals (n = 156) for SLN localization Patients were treated between April 2000 and January 2006	United Kingdom
Hayashida et al. 2010[16]	To determine whether blue dye or radioisotope was superior for a tracer for SLN biopsy	Number of patients: 640 Cancer type: Clinically node-negative breast cancer with Tis or T1 to T3 tumours	Prospective cohort of patients who underwent SLNB at the Keio University Hospital between 2001 and 2006	Japan

Table 5: Objective and Details of Study Design of the Included Primary Studies				
Study	**Objective**	**Population**	**Study Design**	**Location**
Usmani et al. 2010[17]	To evaluate the efficacy of SLNB using imaging, gamma probe, and blue dye for surgical planning of breast cancer	Number of patients: 52 Cancer type: Early invasive breast cancer with clinical staging T1 to T3, which had not spread to lymph nodes or other distant areas	Prospective cohort of consecutive patients between September 2005 and December 2007	Kuwait
Yalcin et al. 2010[18]	To compare the effectiveness of ^{99m}Tc-HIG and ^{99m}Tc-nanocolloid in identifying SLN	Number of patients: 50 Cancer type: Early invasive breast cancer (T1 or T2 that had not spread to lymph nodes)	Prospective cohort of patients who visited the study centre between 2004 and 2008	Turkey
Hojo et al. 2010[19]	To evaluate the performance of a fluorescent dye in combination with a radioisotope or dye for the selection of targets for SLNB in patients with breast cancer	Number of patients: 141 Cancer type: Clinically node-negative breast cancer	Prospective cohort of patients who were examined from August 2006 to December 2008 at National Cancer Center Hospital	Japan
Dixon et al. 2009[20]	To determine if immediate preoperative injection of radiopharmaceutical and blue dye produces a satisfactory rate of sentinel node detection and if it accurately identifies nodes involved with cancer	Number of patients: 163 Cancer type: Clinically node-negative invasive breast cancer	Prospective cohort of patients undergoing breast-conserving procedures between December 2005 and December 2007	United Kingdom
Mathelin et al. 2009[21]	To assess the safety and efficacy of methylene blue dye compared with radioisotope in mapping of SLNs	Number of patients: 100 Cancer type: Invasive breast cancer or DCIS	Prospective cohort of patients enrolled between April 2006 and April 2007	France
Koukouraki et al. 2009[22]	To evaluate the identification rate of combined blue dye and radioisotope compared with dye mapping alone in patients with breast cancer	Number of patients: 501 Cancer type: Invasive breast cancer	Patients hospitalized between 1997 and 2006 in the surgery department of the University Hospital of Crete Unclear if prospective or retrospective study	Greece

Table 5: Objective and Details of Study Design of the Included Primary Studies				
Study	**Objective**	**Population**	**Study Design**	**Location**
Noguchi et al. 2009[23]	To evaluate whether a combination of peritumoural injection of radioisotope and subareolar injection of blue dye improves the identification rate of SLNs	Number of patients: 201 Cancer type: Non-invasive or invasive breast cancer	Prospective cohort of patients identified between August 2006 and December 2008	Japan
Kargozaran et al. 2007[24]	To compare the successful rate of SLN identification with peritumoural injection of ^{99m}Tc-sulphur colloid and subareolar blue dye injection	Number of patients: 124 Cancer type: Stage I or II invasive breast cancer	A cohort of patients who were diagnosed with invasive breast cancer between March 2003 and August 2006 and underwent mastectomy Not clear if prospective or retrospective	United States
Argon et al. 2006[25]	To evaluate methods of identification of the SLN using ^{99m}Tc-tin colloid and isosulfan blue dye	Number of patients: 100 Cancer type: Clinically node-negative T1 to T2 breast cancer	A cohort of patients admitted to Ege University Hospital for surgery Not clear if prospective or retrospective The time period over which data were collected was not reported	Turkey
D'Eredita et al. 2006[26]	To provide further validation of the subareolar injection technique for SLN identification	Number of patients: 195 Cancer type: Localized breast cancer	A cohort of patients with a diagnosis of invasive breast cancer between January 1999 and September 2004 Not clear if prospective or retrospective	Italy
Goyal et al. 2006[27]	To determine the detection and false-negative rates of SLNB and evaluate factors influencing them	Number of patients: 842 Cancer type: Clinically node-negative breast cancer	Prospective study of patients with early breast cancer enrolled by 31 surgeons, in 18 centres between February 1998 and December 2001, who were participating in an RCT to compare SLNB and ALND	United Kingdom
Kesmodel et al. 2006[28]	To compare peritumoural and subareolar administration of isotope in combination with blue dye for identification of SLN and examine their relative contribution of SLN identification	Number of patients: 456 Cancer type: Invasive breast cancer, clinical state T1 to T4 that had not spread to lymph nodes or other distant areas	Retrospective cohort of consecutive patients who underwent SLN mapping with isotope and blue dye between November 1998 and December 2002 at the Hospital of the University of Pennsylvania	United States

Table 5: Objective and Details of Study Design of the Included Primary Studies				
Study	**Objective**	**Population**	**Study Design**	**Location**
Knauer et al. 2006[29]	To confirm the feasibility and accuracy of SLN biopsy in multicentric breast cancer	Number of patients: 142 Cancer type: Multicentric invasive breast cancer	Analysis of data prospectively collected in a multi-centre database between September 1996 and November 2004	Austria
Takei et al. 2006a[30]	To compare the effectiveness of ^{99m}Tc-HSA and ^{99m}Tc-phytate in combination with blue dye in SLNB for breast cancer	Number of patients: 533 Cancer type: Clinically node-negative breast cancer	Retrospective cohort of consecutive patients who underwent SLNB using a combination of blue dye and isotope between January 2000 and April 2003	Japan
Takei et al. 2006b[31]	To determine whether the presence of blue nodes or hot nodes affected the results of SLN biopsies	Number of patients: 305 Cancer type: Clinically node-negative with Tis or T1 to T3 breast cancers	A cohort of 305 consecutive patients who underwent SLNB with a combination of blue dye and isotope, followed by ALND between November 2001 and June 2003 Not clear if prospective or retrospective	Japan

ALND = axillary lymph node dissection; DCIS = ductal carcinoma in situ; HIG = human polyclonal immunoglobin; HSA = human serum albumin; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy; ^{99m}Tc = technetium-99m.

Systematic reviews

Table 6: Outcomes, Conclusions, and Limitations of the Included Systematic Reviews

Report	Results	Authors' Conclusions	Limitations
Spillane et al. 2011[6]	**Radiocolloid alone** • Multifocal tumours only ▪ Sensitivity — NR ▪ FNR — 0% ▪ NPV — NR ▪ Accuracy — NR • Multicentric or multifocal tumours together ▪ Sensitivity — 92.3% to 92.9% ▪ FNR — 7.1% to 7.7% ▪ NPV — 84.4% to 96.8% ▪ Accuracy — 96.8% to 97.7% **Radiocolloid with blue dye** • Multifocal tumours only ▪ Sensitivity — 78.9% to 100% ▪ FNR — 0% to 33% ▪ NPV — 60% to 100% ▪ Accuracy — 78% to 100% • Multicentric tumours only ▪ Sensitivity — 92.3% to 100% ▪ FNR — 0% to 7.7% ▪ NPV — 90% to 100% ▪ Accuracy — 95.5% to 100% • Multicentric or multifocal tumours together ▪ Sensitivity — 75% to 100% ▪ FNR — 0% to 25% ▪ NPV — 60% to 100% ▪ Accuracy — 8.2% to 16.7% • Large tumours ▪ Sensitivity — 83.8% to 97% ▪ FNR — 16.2% to 3.0% ▪ NPV — 68.4% to 93.2% ▪ Accuracy — 88% to 97.7%	"Based on limited evidence, success rate and FNR appear to be similar to those for small unifocal cancers" p. 383.[6]	Grey literature search did not appear to be performed. Failure to report results of critical appraisal. Generalizability to other tumour types is unknown. Pooling of data was not attempted due to heterogeneity. The details of the radioisotope that was used for SLN identification were not provided. Simply described as "radiocolloid." Unclear if an a priori research protocol was followed in conducting this systematic review. Results of the quality assessment of the included studies were not reported.

Table 6: Outcomes, Conclusions, and Limitations of the Included Systematic Reviews			
Report	**Results**	**Authors' Conclusions**	**Limitations**
National Breast and Ovarian Cancer Centre 2008[7]	**FNR:** 8.2% to 16.7% **Sensitivity:** 83.3% to 92% **NPV:** 92.3% to 97%	False negatives can occur at a similar rate with both SLNB and ALND. FNR can be influenced by the experience of the surgeon performing the procedure.	Included study designs were limited to RCTs. Non-randomized studies where patients received both SLNB and ALND could potentially provide relevant information as well. Unclear if an a priori research protocol was followed in conducting this systematic review. Results of the quality assessment of the included studies were not reported in detail.

ALND = axillary lymph node dissection; FNR = false-negative rate; NPV = negative predictive value; NR = not reported; RCTs = randomized controlled trials; SLN = sentinel lymph node; SLNB = sentinel lymph node biopsy.

Primary studies

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
Varghese et al. 2008[15]	**SLN identification rate:*** ^{99m}Tc-nanocolloid and blue dye combined: 98.7% Blue dye alone: 96.5%	Subdermal and subareolar methylene blue is a safe and effective alternative for SLN identification.	The authors report the results of this study as a retrospective analysis of an RCT. No reference is made to the original RCT. Simple randomization was used to assign patients to each group. It is not clear why the number of patients in each group was unbalanced. Two different ^{99m}Tc radiopharmaceuticals were used during the study. It is not clear if both were equally effective, and no subgroup analysis was performed to assess this. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained.
Hayashida et al. 2010[16]	**SLN identification rate:*** ^{99m}Tc-tin colloid:	"A combination of radioisotopes and blue dye is considered to be a more useful methodology for the detection	Patient demographics and exclusion criteria not reported.

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
	94.7% Blue dye: 79.6% ^{99m}Tc-tin colloid and blue dye combined: 97.7% **Agreement:†** Blue node alone: 7.7% Hot node alone: 43.8% Blue and hot node: 48.5%	of SLN than either reagent alone; however, in a situation where one must be selected, radioisotopes would be the better choice" p.114.[16]	
Usmani et al. 2010[17]	**SLN identification rate:*** ^{99m}Tc-nanocolloid: 96% Blue dye: 87% ^{99m}Tc-nanocolloid and blue dye combined: 98%	Conclusions were specific to SLN biopsy with gamma probe.	Concordance between techniques not presented. No information on training and experience of individuals performing mapping. Single-centre study. Not clear whether patients had prior chemotherapy.
Yalcin et al. 2010[18]	**SLN identification rate:‡** ^{99m}Tc-HIG: 92% Blue dye (HIG group): 96% ^{99m}Tc-nanocolloid: 96% Blue dye (nanocolloid group): 100%	No conclusions made with respect to the comparative effectiveness of ^{99m}Tc and blue dye.	Unclear if consecutive patients or how patients were selected. Concordance of techniques not presented. Unclear as to how patients were assigned to receive ^{99m}Tc-nanocolloid or ^{99m}Tc-HIG. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained.

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
Hojo et al. 2010[19]	**SLN identification rate:*** ^{99m}Tc-phytate: 100% Blue dye: 92.9%	No conclusions made with respect to the comparative effectiveness of radiopharmaceutical and blue dye.	Inclusion and exclusion criteria not stated. Unclear if all patients examined during the study period were enrolled or whether any method of selection was applied. ^{99m}Tc-phytate and blue dye were used for mapping in two different groups of patients. It is unclear how patients were assigned to each group. Non-random assignment to treatment could lead to bias and confounding. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained. Not all patients received ^{99m}Tc and blue dye, so concordance between the techniques could not be determined.
Dixon et al. 2009[20]	**SLN identification rate:*** ^{99m}Tc-albumin nanocolloid and blue dye combined: 98.8% **Agreement:†** Hot and blue: 74% Hot only: 19% Blue only: 7%	The authors concluded that injection of radiopharmaceutical once the patient is anesthetized is an effective means of identifying SLNs. No conclusions made with respect to the comparative effectiveness of radiopharmaceutical and blue dye.	The identification rates for ^{99m}Tc alone and blue dye alone were not reported, so no comparison can be made. Administration technique for blue dye was changed partway through the study. No analyses were performed to determine how this might affect outcomes. Unclear if all patients examined during the study period were enrolled or whether any method of selection was applied. All procedures were performed by a single surgeon with a licence to administer radiopharmaceuticals. It is unclear whether the results of the study would be generalizable to other surgeons who might not have the same level of specialized training.
Koukouraki et al. 2009[22]	**SLN identification rate:***	The combined technique improves the identification rate of SLNs.	Concordance between techniques not presented. Identification rate with ^{99m}Tc-nanocolloid alone not

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
	Patients with stage T1N0, T2N0 ^{99m}Tc-nanocolloid and blue dye combined: 99.3% Blue dye alone: 95.3% ^{99m}Tc-nanocolloid alone: not reported Patients with advanced disease: Isotope and dye: 100% Blue dye alone: 93.3% ^{99m}Tc-nanocolloid alone: not reported		reported. Method of assigning mapping technique was not reported. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained. Unclear if all patients examined during the study period were enrolled or whether any method of selection was applied.
Mathelin et al. 2009[21]	**SLN identification rate:‡** ^{99m}Tc-colloidal rhenium sulphur alone: 91% Blue dye alone: 99% **Agreement:†** Hot: 94% Blue: 65% Hot and blue: 60% Hot only: 35% Blue only: 6%	Methylene blue dye is safe for identification of sentinel lymph nodes in early breast cancer. No conclusions made with respect to the comparative effectiveness of radiopharmaceutical and blue dye.	Unclear if all patients examined during the study period were screened for enrolment or whether any method of selection was applied. No patients had undergone chemotherapy or radiation. It is not clear if similar findings would be expected in such patients. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained.
Noguchi et al. 2009[23]	**SLN identification rate:*** ^{99m}Tc-phytate and blue dye combined: 99.5% ^{99m}Tc-phytate: 97%	Subareolar injection of blue dye and peritumoural injection of radioisotope improve the SLN identification rate and reduce the false-negative rate of SLN biopsy.	No details on inclusion or exclusion criteria. Unclear if all patients examined during the study period were screened for enrolment or whether any method of selection was applied. No information on training and experience of individuals

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
	Blue dye: 98% **Agreement:**¶ Blue only: 2.5% Hot only: 1.5% **Concordance rate:**§ 93%		performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained. No information on prior treatment, if any.
Kargozaran et al. 2007[24]	**SLN identification rate:*** ^{99m}Tc-sulphur colloid and blue dye combined: 98.4% ^{99m}Tc-sulphur colloid alone: 97.6% Blue dye alone: 92.7% **Concordance rate:**§ 91.9% **Agreement:**‡ Hot only: 5.6% Blue only: 0.8%	Results demonstrate a high rate of SLN identification with subareolar blue dye and peritumoural ^{99m}Tc 99-sulphur colloid used together.	Two surgeons with "extensive experience in SLN biopsies" performed all operations. It is not clear if the study results would be generalizable to less experienced surgeons. All patients had invasive cancer. Unclear if all patients examined during the study period were screened for enrolment or whether any method of selection was applied. No information on previous treatments or exclusion of patients based upon previous treatment.
Argon et al. 2006[25]	**SLN identification rate:*** ^{99m}Tc-sulphur tin alone: 90% Blue dye alone: 88% **Agreement:**¶ Hot only: 12% Blue only: 2%	SLN localization with combined isotope and blue dye is accurate and easy.	Overall identification rate with isotope and blue dye combined not reported. Timing of data collection was not reported. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained.
D'Eredita et	**SLN identification**	Results of the study provide further validation	Only results for Group 1 were applicable to the research

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
al. 2006[26]	**rate:*** Group 1 ^{99m}Tc-human albumin colloid and blue dye combined: 95% Blue dye alone: 94.6% Group 2 Not applicable, as no comparison with isotope Group 3 ^{99m}Tc-human albumin colloid and dye: 100% Blue dye alone: No reported	of the subareolar injection technique. No conclusions made with respect to the comparative effectiveness of radiopharmaceutical and blue dye.	question of this rapid review. Different treatments and techniques were used during different time periods. It is not clear if other differences existed during those time periods that could affect outcomes. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained.
Goyal et al. 2006[27]	**SLN identification rate:*** ^{99m}Tc-albumin colloid and blue dye combined: 96.0% ^{99m}Tc-albumin colloid alone: 85.6% Blue dye alone: 85.6%	The success and accuracy of SLN mapping are optimal when isotope and dye are used in combination.	The surgeons who performed the SLN mapping and biopsy were participating in an RCT. The results presented were for the learning or validation phase for the RCT. It is not clear if the results of the study would be applicable to a "real-world" setting. Concordance between the 2 techniques could not be determined from the data presented. Generalizability to those who had undergone prior radiation or surgery is not known. Previous chemotherapy not reported.
Kesmodel et al. 2006[28]	**Peritumoural isotope:** **SLN identification rate:*** ^{99m}Tc-sulphur colloid alone: 97%	Results suggest that independent of the site of injection, isotope is essential for SLN mapping.	No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained.

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
	Blue dye alone: 96% **Concordance:**[§] 93% **Agreement:**[†] Hot and blue: 73% Hot only: 23% Blue only: 4% **Subareolar isotope:** **SLN identification rate:*** ^{99m}Tc sulphur colloid alone: 98% Blue dye alone: 88% **Concordance:**[§] 89% **Agreement:**[†] Hot and blue: 81% Hot only: 19% Blue only: 0.2%		Previous treatments for breast cancer were not reported.
Knauer et al. 2006[29]	**Agreement:**[¶] Blue and hot nodes: 67.9% Blue only: 9.0% Hot only: 3.8%	SLN biopsy in multicentric cancer is indicated, but should still be performed in the context of a clinical study.	Concordance could be determined only for the 78 patients who received isotope and blue dye. All patients had multicentric cancer. Generalizability to other cancer types is unclear. Limited information on administration of isotope and dye. Two different types of blue dye were used. It is not clear if similar results would be expected if the concordance for each dye was determined separately.
Takei et al. 2006a[30]	**SLN identification rate:*** HSA Group: ^{99m}Tc and blue dye	Results suggest that ^{99m}Tc-phytate is a better radioactive agent than ^{99m}Tc-HSA for SLN biopsy in breast cancer.	The two isotopes were used during different time periods. The individual or individuals performing the mapping with phytate may have had more experience, as it was used

Table 7: Outcomes, Conclusions, and Limitations of the Included Primary Studies			
Study	**Outcomes**	**Authors' Conclusions**	**Limitations**
	combined: 97% Blue dye only: 94.7% ^{99m}Tc only: 89.5% Phytate Group: ^{99m}Tc and blue dye combined: 99.6% Blue dye only: 97.1% ^{99m}Tc only: 95.6%		later in the cohort. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained. No information on prior treatment, if any. No details of inclusion or exclusion criteria.
Takei et al. 2006b[31]	**Agreement:**¶ Blue node: 96.8% Hot node: 95.8% Blue or hot: 99.4% Hot only: 3.6% Blue only: 2.6%	"All blue nodes and hot nodes should be harvested when a combination technique is applied" p.185.[31]	Not clear if prospective or retrospective. No details of inclusion or exclusion criteria. No information on training and experience of individuals performing mapping. The number of individuals performing the mapping was not reported. Learning curve effects could not be ascertained. No information on prior treatment, if any.

HIG = human polyclonal immunoglobulin; HSA = human serum albumin; RCT = randomized controlled trial; SLN = sentinel lymph node; ^{99m}Tc = technetium-99m.
*Percentage of patients in whom one or more sentinel nodes was successfully identified.
†Percentage of the identified SLNs. Multiple SLNs were identified in some patients.
‡Percentage of tumours for which the sentinel nodes were successfully identified. Some patients had more than one tumour.
§Percentage of patients with at least one SLN that was hot and blue.
¶Percentage of patients, not percentage of nodes.

Appendix 5: Exclusion Criteria and Demographic Characteristics

Table 8: Exclusion Criteria and Patient Characteristics of Included Studies

Study	Exclusion Criteria	Demographics
Varghese et al. 2008[15]	• Tumours > 2 cm on ultrasound assessment • Clinical or radiological evidence of axillary lymph node involvement • Previous operation in the breast or axilla • Neoadjuvant chemotherapy • Refusal of the procedure by the patients	Methylene blue only: Age: mean — 58.3 years Type of cancer: Infiltrating ductal carcinoma — 63% Infiltrating lobular carcinoma — 4% Mixed – 9% DCIS — 24% LCIS — 0.5% Methylene blue and isotope combined: Age: mean — 58.5 years Type of cancer: Infiltrating ductal carcinoma — 60% Infiltrating lobular carcinoma — 4% Mixed — 2% DCIS — 33% LCIS — 0.5%
Hayashida et al. 2010[16]	• Not stated	Not reported
Usmani et al. 2010[17]	• Clinical evidence of axillary metastases • Previous axillary lymphadenectomy • Locally advanced disease • Treatment with chemotherapy or radiotherapy prior to breast surgery • Pregnancy or lactation	Age: mean — 47.3 years Histological site: Ductal infiltrating — 75% Lobular infiltrating — 8% Medullary carcinoma — 12% Invasive mucinous carcinoma — 6%
Yalcin et al. 2010[18]	• Palpable axillary lymph nodes • Surgery or excision biopsy in the involved breast • Multifocal or multicentric tumours • Adjuvant systemic treatment before surgery	Age: mean — 53.5 ± 12.2 years Histological diagnosis: Invasive ductal carcinoma — 64% Intraductal carcinoma — 16%

Table 8: Exclusion Criteria and Patient Characteristics of Included Studies		
Study	**Exclusion Criteria**	**Demographics**
	• Pregnancy	Invasive lobular carcinoma — 12% Infiltrative carcinoma — 8%
Hojo et al. 2010[19]	• Not stated	Age: mean — 59.4 years Tumour classification: Tis — 23.4% T1 — 40.4% T2 — 36.2%
Dixon et al. 2009[20]	• Not stated, but report states that no patients were excluded based upon tumour size or previous surgical intervention.	Age: median – 63 years No other characteristics reported
Koukouraki et al. 2009[22]	• Previous axillary or major breast surgery • Multicentric breast cancer • Pregnancy • Previous radiotherapy	Age: Median — 56.3 Pathology: Invasive ductal carcinoma — 85% Lobular invasive carcinoma — 6.6% Others — 8.4%
Mathelin et al. 2009[21]	• Suspect axillary lymph nodes • Deficiency of glucose-6-phosphate dehydrogenase • Thalassemia or drepanocytosis	Age: mean — 58 ± 10.8 years DCIS: 2.9% Invasive carcinomas: 97.1% Grade of invasive carcinomas: Low — 37% Intermediate — 41% High — 22%
Noguchi et al. 2009[23]	• Not stated	Age: mean — 55.7 years Histological tumour type: Special types — 7.5% Non-invasive ductal carcinoma — 9.5% Invasive ductal carcinoma — 83%

Table 8: Exclusion Criteria and Patient Characteristics of Included Studies		
Study	**Exclusion Criteria**	**Demographics**
Kargozaran et al. 2007[24]	• DCIS	Age: mean — 58.7 years Tumour type/histology not reported.
Argon et al. 2006[25]	• Previous treatment with radiotherapy, chemotherapy • Prior axillary surgery • Multiple primary tumours	Age: mean — 49.2 years Tumour type: Invasive ductal carcinoma — 65% Invasive lobular carcinoma — 9% DCIS — 12% Other — 14%
D'Eredita et al. 2006[26]	• Palpable axillary nodes • Ductal in situ histological results • Previous radiotherapy to the breast • Prior axillary surgery • Pregnancy	Age: mean — 57.6 years Tumour histology: Invasive ductal — 50% Invasive lobular — 7% Invasive ductal + DCIS — 30% Other invasive — 13%
Goyal et al. 2006[27]	• Pregnancy • Known multicentric cancer • Prior ipsilateral axillary surgery or breast surgery, except previous benign biopsy • Previous irradiation of the ipsilateral axilla or breast • Pre-existing limb disease causing swelling • Known allergy to human albumin or Patent Blue V	Age: median — 57 years Pathological findings: Invasive ductal — 74.4% Invasive lobular — 10.9% Other — 14.7%
Kesmodel et al. 2006[28]	• Not stated	Age: Subareolar isotope — median 52 years Peritumoural isotope — median 55 years Tumour histology — Subareolar isotope: Invasive ductal — 73% Invasive lobular — 10% Other — 15% Unknown — 2% Tumour histology — Peritumoural isotope:

Table 8: Exclusion Criteria and Patient Characteristics of Included Studies		
Study	**Exclusion Criteria**	**Demographics**
		Invasive ductal — 81% Invasive lobular — 10% Other — 9% Unknown — 0%
Knauer et al. 2006[29]	• Not stated	Age: mean — 56.6 years Tumour histology Ductal ± DCIS — 77.5% Lobular — 17.6% Other — 2.8% DCIS + microinvasion — 2.1%
Takei et al. 2006a[30]	• Not stated	Age: Mean HSA group — 54.7 years Age: Mean phytate group — 55.2 years Histological type: DCIS — 8.7% Invasive carcinoma — 83.3% Others — 8.0%
Takei et al. 2006b[31]	• Not stated	Mean: 55.2 years Tumour classification: Tis — 7.5% T1 — 26.6% T2 — 60.1% T3 — 5.8%

Cm = centimeter; DCIS = ductal carcinoma in situ; HSA = human serum albumin; LCIS = lobular carcinoma in situ; Tis = cancer is in situ; T1 = tumour is ≤ 2 cm across; T2 = tumour is > 2 cm but ≤5 cm across; T3 = tumour is > 5 cm across.

Appendix 6: Techniques

Table 9: Methodology for Radiopharmaceutical and Blue Dye Techniques

Study	Radiopharmaceutical Technique	Blue Dye Technique	Additional Details
Varghese et al. 2008[15]	10 MBq ^{99m}Tc-nanocolloid on the day of surgery or 40 MBq ^{99m}Tc-Albures for those having surgery the following day, injected in the subareolar region	1% methylene blue injected in the subareolar region 10 to 15 minutes before skin incision Breast massaged for 1 to 2 min	Patients randomized to ^{99m}Tc-based radiopharmaceutical or blue dye.
Hayashida et al. 2010[16]	A total of 1.8 mL ^{99m}Tc-tin colloid (74 MBq/mL) injected at 3 points around the tumour and subdermally just above the tumour on the day before surgery	2.5 mL isosulfan blue dye injected after the induction of general anesthesia, peritumourally and subdermally	All patients underwent mapping with both ^{99m}Tc and blue dye.
Usmani et al. 2010[17]	37 MBq ^{99m}Tc-nanocolloid intradermally injected in the peritumoural region of each palpable tumour or above and below the scar in cases of patients who had had an excision biopsy Timing of injection relative to surgery not reported	2 mL to 5 mL isosulfan blue vital dye injected in the subareolar region, outside the areolar border 10 to 15 min before surgery Gentle massage for 5 min at the site of the injection	All patients underwent mapping with both ^{99m}Tc and blue dye.
Yalcin et al. 2010[18]	111 MBq ^{99m}Tc-HIG or ^{99m}Tc-nanocolloid injected at 4 points around the tumour or biopsy scar Timing of injection relative to surgery not reported	1% isosulfan blue dye injected in the same manner as Tc-99m 10 to 15 minutes before the incision was made	All patients underwent mapping with both ^{99m}Tc and blue dye. No details were provided as to how patients were selected to receive ^{99m}Tc-nanocolloid or HIG.
Hojo et al. 2010[19]	30 to 80 MBq ^{99m}Tc-phytate injected intradermally into the area overlying the tumour and subareolar region 1 day prior to surgery	2 mL patent blue dye injected into the subareolar region and skin overlying the tumour after the induction of anesthesia. Whole breast compressed and massaged for about 5 min	Two groups of patients, one of which underwent mapping with blue dye and fluorescent dye and one of which underwent mapping with ^{99m}Tc-phytate and fluorescent dye. The number of patients in each group or method of assigning mapping method was not reported.
Dixon et al. 2009[20]	25 MBq ^{99m}Tc-albumin nanocolloid injected subcutaneously at the six o'clock position of the nipple areolar complex following induction of anesthesia	First 48 patients: 2 mL patent blue-V sodium 2.5% diluted to 5 mL with sodium chloride injected into the subareolar region	All patients underwent mapping with both ^{99m}Tc and blue dye.

Table 9: Methodology for Radiopharmaceutical and Blue Dye Techniques			
Study	**Radiopharmaceutical Technique**	**Blue Dye Technique**	**Additional Details**
		Remaining patients: following injection of radiopharmaceutical, 1 to 2 mL undiluted dye injected, followed by 3 mL sodium chloride. Breast massaged for 60 seconds	
Koukouraki et al. 2009[22]	37 to 111 MBq ^{99m}Tc-nanocolloid injected into the subareolar lymphatic plexus on the day before or the day of surgery	4 mL isosulfan blue dye injected into the subareolar area after the induction of general anesthesia	250 patients underwent mapping with blue dye alone; 251 had ^{99m}Tc-nanocolloid and blue dye combined. The method of assigning mapping method was not reported.
Mathelin et al. 2009[21]	15 MBq to 28 MBq ^{99m}Tc-colloidal rhenium sulphur injected into 4 cardinal points in the subareolar area 18 hours prior to surgery	2 mL methylene blue dye injected at the 4 cardinal points 10 min prior to surgery without massage	All patients underwent mapping with both ^{99m}Tc and blue dye.
Noguchi et al. 2009[23]	2 mCi ^{99m}Tc-phytate injected peritumourally in 2 separate sites 12 hours before surgery.	2 mL patent blue dye injected intraoperatively in the subareolar location, and the breast was massaged for 5 min	All patients underwent mapping with both ^{99m}Tc and blue dye.
Kargozaran et al. 2007[24]	37 MBq ^{99m}Tc-sulphur colloid injected in 6 separate peritumoural sites 1 hour before of surgery.	3 mL to 5 mL lymphazurin injected in the subareolar location intraoperatively, and the breast was massaged for 5 min	All patients underwent mapping with both ^{99m}Tc and blue dye.
Argon et al. 2006[25]	37 MBq ^{99m}Tc-tin colloid injected at 4 periareolar sites intradermally on the day prior to surgery	2 mL isosulfan blue dye was injected peritumourally or into the biopsy cavity The injection site was massaged for about 5 min	All patients underwent mapping with both ^{99m}Tc and blue dye.
D'Eredita et al. 2006[26]	**Group 1:** Patients who were treated from January 1999 to December 2001 • 8 to 12 MBq ^{99m}Tc-labelled human albumin colloid particles injected in 4 peritumoural sites immediately around the breast lesion on the day before surgery **Group 2:** Patients who were treated from	**Group 1:** 4mL methylene blue dye injected subdermally above the breast mass 10 to 20 min before axillary incision **Group 2:** 4 mL methylene blue dye injected into the upper outer edge of the areola 10 to 20 min before axillary incision	Patients in groups 1 and 3 underwent mapping with both ^{99m}Tc and blue dye. Patients in group 2 underwent mapping with blue dye alone.

Table 9: Methodology for Radiopharmaceutical and Blue Dye Techniques			
Study	**Radiopharmaceutical Technique**	**Blue Dye Technique**	**Additional Details**
	January 2002 to October 2002 • No radiopharmaceutical **Group 3:** Patients who were treated from November 2002 to September 2004 • 8 to 12 MBq ^{99m}Tc-labelled human albumin colloid particles injected as 4 subdermal injections in the skin immediately above the breast lesion	**Group 3:** 4 mL methylene blue dye injected into the upper outer edge of the areola 10 to 20 min before axillary incision	
Goyal et al. 2006[27]	40 MBq ^{99m}Tc-albumin colloid injected at 4 sites peritumourally on the day before surgery or 20 MBq injected on the day of surgery	2 mL patent blue V dye injected peritumourally 3 to 5 minutes before the first incision was made	All patients underwent mapping with both ^{99m}Tc and blue dye.
Kesmodel et al. 2006[28]	1.0 mCi of ^{99m}Tc-labelled sulphur colloid injected on the day of surgery either using either a subareolar or peritumoural technique	3mL 1% isosulfan blue dye injected after the induction of anesthesia No massage performed	All patients underwent mapping with both ^{99m}Tc and blue dye.
Knauer et al. 2006[29]	^{99m}Tc-nanocolloid was used, but no additional details of injection technique or timing of injection were reported	2 mL to 5 mL vital blue dye or patent blue V Guerbet was used, but no additional details of injection technique or timing of injection were reported	10 patients had ^{99m}Tc alone, 54 had blue dye alone, and 78 had both.
Takei et al. 2006a[30]	Patients treated prior to November 2001: 1 mL of 0.5 mCi of ^{99m}Tc-HSA injected subdermally above the tumour on the morning of surgery Patients treated after November 2001: 1 mL of 0.5 mCi of ^{99m}Tc-phytate injected subdermally above the tumour on the morning of surgery.	2.0 mL to 2.5 mL patent blue V solution injected subdermally above the tumour after the induction of anesthesia Breast was compressed and massaged for about 5 minutes	All patients underwent mapping with both ^{99m}Tc and blue dye.
Takei et al. 2006b[31]	1 mL of 0.5 mCi of ^{99m}Tc-phytate injected subdermally 1 to 7 hours preoperatively	2.0 mL to 2.5 mL patent blue V solution injected subdermally after the induction of anesthesia	All patients underwent mapping with both ^{99m}Tc and blue dye.

HIG = human polyclonal immunoglobin; HSA: human serum albumin; MBq = megabecquerel; mCi = millicurie; ^{99m}Tc = technetium-99m

APPENDIX 2.17

INDICATION OVERVIEW

Obstructive uropathy can be defined as any blockage of urine drainage from the kidney (renal calyces or renal pelvis), ureter, or bladder.[1] As a result of the blockage, urine backs up into the kidneys, causing dilatation of the ureter, renal pelvis, and renal calyces, which can damage the kidney if it is not treated. The appearance of dilated or enlarged renal pelvis and calyces is referred to as hydronephrosis and is a symptom of obstructive uropathy.[2] Obstructive uropathy can be a long-term disease (chronic) or occur suddenly (acute). As well, it can occur in one kidney (unilateral) or both kidneys (bilateral).[2] Symptoms may include nausea, vomiting, excessive sweating (diaphoresis), and abdominal or groin pain.[3]

There are many causes of obstructive uropathy; however, the most common causes include stones in kidneys (nephrolithiasis),[4] ureter (ureterolithiasis) or anywhere in the urinary tract (urolithiasis).[5,6] Other causes of obstructive uropathy include health conditions such as pregnancy, prostate cancer,[2] retroperitoneal fibrosis,[7] spinal cord injury,[8,9] ureteral stricture,[6] and congenital anomalies (e.g., ureteropelvic junction obstruction [UJO]),[5,10] which is most common in children but also occurs in adults.[6] The gold standard to assess urinary obstruction is unclear;[11-13] therefore, several imaging modalities are often used.[8]

Population: Adults and children with chronic and acute urinary obstruction presenting with symptoms including renal colic, suspected urinary obstruction symptoms (e.g., evidence of hydronephrosis), impaired renal function.

Intervention: Renal scintigraphy (renal scan). Synonyms for renal scan in the literature and in clinical practice include diuresis renography, renal flow studies, radioisotope renography,[8] Lasix renography (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011), and nuclear medicine renogram.[14] The terms renal scintigraphy and renal scan will be used throughout this report.

Renal scanning begins with intravenous (IV) administration of a radiotracer immediately followed by acquisition of images for 20 to 30 minutes.[15] An external gamma camera detects emission of gamma rays emitted by the radiotracer, which is reflective of the distribution of radiotracer in the patient. Radiotracers currently used in Canada include technetium-99m-labelled mercaptoacetyl trigylcine (^{99m}Tc-MAG3), technetium-99m-labelled- diethylenetriamine pentaacetic acid acid (^{99m}Tc-DTPA), or technetium-99m-labelled-dimercaptosuccinic acid (^{99m}Tc-DMSA).

^{99m}Tc-MAG3 and ^{99m}Tc-DTPA are rapidly taken up by the kidney and then excreted through the urinary tract. Their mechanism of renal uptake and imaging characteristics, however, differ — ^{99m}Tc-DTPA is taken up by the kidney through glomerular filtration and is not secreted or reabsorbed by the renal tubules, whereas ^{99m}Tc-MAG3 is mostly taken up by the proximal renal tubules and its high plasma protein binding prevents it from being filtered through the glomerular membrane. Once ^{99m}Tc-DTPA reaches the kidney, it is then excreted by filtration. Hence, the glomerular filtration rate (GFR) quantifies the amount of filtrate formed per minute (normal GFR:

~ 120 mL/min in adults). Conversely, clearance of ^{99m}Tc-MAG3 is expressed as the effective renal plasma flow (ERPF) — an approximation of renal plasma flow (normal ERPF: ~ 600 mL/min in adults). ^{99m}Tc-DMSA remains in the renal parenchyma for an extended period and is used for static renal scintigraphy. ^{99m}Tc-DMSA accumulates in the functioning renal cortex, and impaired renal cortex and space-occupying lesions are depicted as hypoactive areas.[16]

The diuretic, furosemide (Lasix), is then administered by IV, and a second series of images is acquired for an additional 20 to 30 minutes while the bladder empties.[15] The images gathered as the bladder empties help to calculate a filtration rate that provides information regarding how well the kidney is functioning and if there is an obstruction.[17] These images are used to calculate the clearance rate of the radiotracer, which is measured by the following outcomes: renal transit time (RTT),[14] and washout half-time ($T_{1/2}$).[18,19] If the patient has problems emptying his or her bladder, a urinary catheter may be used.[16]

Comparators: For this report, the following diagnostic tests are considered as alternatives to renal scintigraphy:

- *Magnetic Resonance Urography (MRU):* MRU requires a magnetic resonance (MR) scanner. Patients undergoing MRU are given fluids to hydrate the body. A sedative may be administered (usually in children) at this point, and a catheter (usually in children) may also be given to the patient so that the flow of urine can be observed without the patient having to go to the washroom during the procedure. A diuretic, typically furosemide (Lasix) is administered and images are taken with the MRI machine. A contrast agent (gadolinium [Gd]) is also administered, usually 15 minutes after the diuretic, and more images are taken to measure the volume of the kidney and how the urine accumulates, in order to calculate measurements that determine the renal function.[12,14,20]
- *Ultrasound (U/S):* During a U/S, a transducer is placed over the organ of interest. The transducer produces sound waves that pass through the body. As the sound waves pass through the body, they produce echoes that are analyzed by a computer to produce images of the body part being analyzed.[21] When there is a presence of obstruction in the renal tract, obstruction is diagnosed primarily by the appearance of hydronephrosis (expert opinion — Martin Reed). Obstruction in the kidney may also cause a decrease in blood flow that can be measured as an increase in vascular resistance (arterial resistance),[17,18] referred to as the renal resistive index (RI). Generally, an RI less than or equal to 0.70 means kidney function is normal,[9,17] while an RI greater than 0.70 suggests an obstructed kidney.[22] In children younger than six months, an RI greater than 0.9 is borderline obstructive hydronephrosis.[18] Doppler ultrasound, which is a type of ultrasound that shows images in colour, can distinguish between obstructive and non-obstructive pyelocaliectasis[17] and show a wave-like (peristaltic)[23] inflow into the bladder (ureterovesical or urinary jet). If a urinary jet is absent, this can also be indicative of obstruction.[17,19] Relative jet frequency is the measure used to diagnosis presence of jets indicative of obstruction.[19]

Other possible comparators could include the Whitaker test, which has been largely replaced by computed tomography (CT) and U/S (expert opinion — Martin Reed and Eric Turcotte). Retrograde pyelography is a surgical technique and is used primarily for cancer diagnosis rather than obstruction assessment (expert opinion — Martin Reed and Eric Turcotte). Both of these comparators were excluded from this report. Renal scan with ^{123}I-orthoiodohippurate (*^{123}*I-OIH) uses the same approach as the ^{99m}Tc-based renal scan.[24] No information regarding ^{123}I-OIH renal scan related to the criteria was identified in the literature. (Note: ^{123}I-OIH is not currently

available on the Canadian market and when it was, the $T_{1/2}$ of 13 hours limited its availability; expert opinion —Gilbert Matte.)

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities
- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and obstructive uropathy.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials, and non-randomized studies, including diagnostic accuracy studies. No date or human limits were applied to the HTA/SR/MA search. For primary studies, the retrieval was limited to documents published between January 1, 2001 and April 1, 2011, and the human population. Both searches were also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified that addressed specific criteria, experts were consulted.

SEARCH RESULTS

The literature search identified 34 HTA/SR/MA and 816 primary studies. From the HTA/SR/MA, 13 potential articles underwent full-text screening. From the primary studies, 142 articles underwent full-text screening.

No applicable HTA/SR/MA were identified with information to address Criterion 7 on the relative diagnostic accuracy of tests. Eight applicable primary studies were identified for this criterion (three relevant for adult population and five relevant for children), and 32 articles reported information for the following criteria: 1) Size of the affected population; 2) Timeliness and urgency of test results in planning patient management; 3) Impact of not performing a diagnostic imaging test on mortality related to the underlying condition; 4) Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition; 5) Relative impact on health disparities; 6) Relative patient acceptability of test; 8) Relative risks associated with the test; and 9) Relative availability of expertise and experience required for the test.

The remaining citations were either articles found through searching the grey literature, articles from targeted searches, or articles from the reference lists.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	**Adult** The prevalence of obstructive uropathy ranges from 5 in 10,000 to 5 in 1,000, depending on the type of obstructive uropathy.[4,5,25,26] **Pediatric** The most common cause of obstructive uropathy in children is due to UJO and it occurs in 1 in 1,500 children.[10] Assuming the incidence rate in Canada is similar to that in the United States, the size of the affected population is more than 1 in 10,000 (0.01%) and less than or equal 1 in 1,000 (0.1%) in both the adult and pediatric populations.
2	**Timeliness and urgency of test results in planning patient management**	According to the Saskatchewan Ministry of Health, the priority for renal scan for the evaluation of hydronephrosis is two to seven days, and eight to 30 days for GFR and ERPF measures for suspected urinary tract obstruction and impaired renal function (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). **Adult** Acute bilateral obstruction symptoms will disappear within hours or days if the disease is detected and treated promptly.[4] In chronic cases of obstruction, immediate interventions are not necessary, except in cases where an infection needs to be drained or there is a solitary kidney.[27] **Pediatric** No pediatric-specific urgency classification for suspected obstructive uropathy was listed (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011); however, based on possible morbidities associated with a delay in diagnosis, the target time frame would be at a minimum similar to that of adults. UJO in children may resolve spontaneously within the first 18 months of life.[10,28] The target time frame for performing the ^{99m}Tc-based test is between 8 and 30 days, and obtaining the test results in the appropriate timely manner for the underlying condition has moderate impact on the management of the condition or the effective use of heath care resources.

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria Related to the Underlying Health Condition		
Criterion		**Synthesized Information**
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	According to Statistics Canada, 52 patients died from obstructive uropathy (1.6 per million people) and 39 due to urolithiasis (1.2 per million) in 2007 (ages not specified).[29] Diagnostic imaging results have no impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	**Adult** Renal obstruction longer than one week can cause permanent renal damage but with recovery in renal function.[7] Complete obstruction of more than 12 weeks can cause irreversible damage to the renal system[7] and, potentially, chronic kidney failure.[30] Other potential comorbidities from renal obstruction include chronic tubulointerstitial disease,[7] urinary retention,[26] chronic/recurrent UTI,[5] incontinence,[26] and complications from long-term catheter use.[26] In chronic bilateral obstruction, once the blockage is cleared, patients may experience "post-obstructive" diuresis, which can be life-threatening.[26] **Pediatric** 23% of children with renal insufficiency will require transplantation.[30] Diagnostic imaging test results can have a moderate impact on morbidity or quality of life.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	*Renal scintigraphy:* Patients may have concerns about radiation exposure and the IV injection of a radiopharmaceutical agent. IV fluids might be required if the adequacy of hydration is a concern.[16] Because a full bladder may slow drainage of the radiopharmaceutical from the upper part of urinary tract, the bladder should be emptied frequently. Bladder catheterization may be required, especially in pediatric patients. In particular in children, catheterization may be associated with some discomfort.[31]

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>MRU: MRU is an MRI technique. Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. This may be less of a problem with new MRI machines, if available (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[32,33] Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

Children may require sedation and catheterization for the duration of the MRU procedure.[14] Patients may also have difficulties accepting the contrast dye, if required.[33,34]

U/S: This test may be preferred in pediatric patients, as there is no radiation and does not require sedation of children.

Renal scintigraphy using ^{99m}Tc-radiolabelled isotopes:
• is minimally less acceptable than MRU in adult patients
• is moderately more acceptable than MRU in pediatric patients
• is minimally less acceptable than U/S in both adult and pediatric patients.</td></tr>
<tr><td>7</td><td>Relative diagnostic accuracy of the test</td><td>Adult
The review of the current literature yielded three primary studies that compared renal scan with various comparators in the diagnosis of renal obstructive uropathy in adults.[8,35,36]

<table>
<tr><th colspan="3">Diagnostic Accuracy of Imaging Tests in Adults</th></tr>
<tr><th>Test</th><th>Sensitivity (%)</th><th>Specificity (%)</th></tr>
<tr><td>MRU</td><td>70 to100</td><td>N/A</td></tr>
<tr><td>U/S</td><td>96</td><td>90</td></tr>
</table>
MRU = magnetic resonance urography; N/A = not available; U/S = ultrasound.</td></tr>
</table>

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>
Pediatric
Five primary studies evaluated diagnostic accuracy of MRU and U/S compared with renal scan in a pediatric population with renal obstructive uropathy.[12,14,18-20]
<table>
<tr><th colspan="5">Diagnostic Accuracy of Imaging Tests in Pediatrics</th></tr>
<tr><th>Test</th><th>Correlation Coefficient (R)*</th><th>Sensitivity (%),</th><th>Specificity (%)</th><th>Accuracy</th></tr>
<tr><td>MRU</td><td>0.96-0.98</td><td>N/A</td><td>N/A</td><td>0.90</td></tr>
<tr><td>U/S</td><td>N/A</td><td>87</td><td>96.4</td><td>N/A</td></tr>
</table>
CT = computed tomography; MRU = magnetic resonance urography; N/A= Not available; U/S = ultrasound
*Between test and renal scan.

Based on the available evidence, in both adults and children, the diagnostic accuracy of renal scintigraphy with ^{99m}Tc radiolabelled tracers is:

moderately better than MRU in both adult and pediatric patients
moderately better than U/S in both adult and pediatric patients.

</td></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>
Non–radiation-related Risks

Renal scan: Adverse events from renal scintigraphy are rare but may include reaction to the radiopharmaceutical, rash, fever, or chills.[37] There is also a relative contraindication in the administration of captopril in patients with a solitary kidney, as it may precipitate transient acute renal failure if the kidneys have physiologically significant renal artery stenosis (MIIMAC expert opinion).

MRU: MRI is often used in conjunction with the contrast agent Gd. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of NSF. The frequency of severe, life-threatening reactions with Gd is extremely rare (0.001% to 0.01%) and the frequency of moderate reactions range are also rare (0.004% to 0.7%).[38] Children may require sedation.

Radiation-related Risks
<table>
<tr><th colspan="2">Effective Doses of Radiation[39-41]</th></tr>
<tr><th>Diagnostic Study</th><th>Average Radiation Dose (mSv)</th></tr>
</table>
</td></tr>
</table>

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><th></th><th>Adult</th><th>Pediatric</th></tr>
<tr><td>Renal scan — ^{99m}Tc-DMSA</td><td>N/A</td><td>0.039[39]</td></tr>
<tr><td>Renal scan — ^{99m}Tc-MAG3</td><td>1 to 10[40]</td><td>0.015,[39] 0.3 to 3[40]</td></tr>
<tr><td>Renal scan — ^{99m}Tc-DTPA</td><td>N/A</td><td>0.012[39]</td></tr>
<tr><td>MRI</td><td>0[40]</td><td>0[39]</td></tr>
<tr><td>U/S</td><td>0[40]</td><td>0[39]</td></tr>
<tr><td>Average background dose of radiation per year</td><td colspan="2">1 to 3.0[42-44]</td></tr>
</table>
MRI = magnetic resonance imaging; MRU = magnetic resonance urography; mSv = millisievert; N/A = not applicable; ^{99m}Tc-DMSA = technetium-99m-labelled-dimercaptosuccinic acid; ^{99m}Tc-DTPA = technetium-99m-labelled-diethylenetriamine pentaacetic acid; ^{99m}Tc-MAG3 = technetium-99m-labelled mercaptoacetyl triglycine; U/S = ultrasound.

There is some concern from physicians that, in patients with poor functioning kidneys, exposure to a radioisotope may further compromise their function.[8]

Overall, renal scintigraphy using ^{99m}Tc radiolabelled isotopes is:
• minimally less safe than MRU in adults patients
• minimally more safe than MRU in pediatric patients
• minimally less safe than U/S in both adult and pediatric patients.
</td></tr>
<tr><td>**9**</td><td>**Relative availability of personnel with expertise and experience required for the test**</td><td>As radionuclide uptake is different in children, as compared to adults, and reader disagreement is more common for younger children, expertise in pediatric imaging is required for renal scintigraphy. In addition, expertise in pediatric MRU is limited.

Assuming the necessary equipment is available, if ^{99m}Tc imaging using renal scintigraphy is not available, it is assumed that:
• fewer than 25% of the procedures for both adult and pediatric patients can be performed in a timely manner using MRU
• more than 95% of the procedures for both adult and pediatric patients can be performed in a timely manner using U/S.</td></tr>
<tr><td>**10**</td><td>**Accessibility of**</td><td>No nuclear medicine cameras are available in the Yukon, Northwest Territories, or Nunavut.[45]</td></tr>
</table>

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td>alternative tests (equipment and wait times)</td><td>No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[46] Across Canada, the average wait time is 9.8 weeks.[47]

U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[47]

Assuming the necessary expertise is available, if ^{99m}Tc imaging using renal scintigraphy is not available, it is assumed that:
25% to 74% of the procedures in both adult and pediatric patients can be performed in a timely manner using MRU
more than 95% of the procedures in both adult and pediatric patients can be performed in a timely manner using U/S.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of scintigraphy with ^{99m}Tc-based radioisotopes to establish whether obstruction is present is $310.45. U/S is a minimally less costly alternative. MRU is a moderately more costly imaging test.

<table><tr><th colspan="3">Relative Costs</th></tr><tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr><tr><td>Renal scintigraphy</td><td>310.45</td><td>Reference</td></tr><tr><td>MRU</td><td>670.15</td><td>+359.70</td></tr><tr><td>U/S</td><td>88.25</td><td>–222.20</td></tr></table></td></tr>
</table>

ERPF = effective renal plasma flow; GFR = glomerular filtration rate; Gd = gadolinium; IV = intravenous; IVP = intravenous pyelogram; MRI = magnetic resonance imaging; MRU = magnetic resonance urography; N/A = not applicable; NSF = nephrogenic systemic fibrosis; RCIN = radiocontrast-induced nephropathy; ^{99m}Tc = technetium-99m; UJO = ureteropelvic junction obstruction; U/S = ultrasound; UTI = urinary tract infection.

CRITERION 1: Size of affected population (link to definition)

Adult
The prevalence of obstructive uropathy ranges from five in 10,000 to five in 1,000, depending on the type of obstructive uropathy.[4,5,25,26] Chronic unilateral obstructive uropathy occurs in five in 1,000 people,[5] while acute unilateral and chronic bilateral obstructive uropathy occurs in one in 1,000 people.[25,26] Acute bilateral obstructive uropathy occurs in five in 10,000 people.[4] The incidence of kidney stones occurs in 2% to 12%[48-52] of the population.

Pediatric
The most common cause of obstructive uropathy in children is due to UJO and it occurs in one in 1,500 children.[10] Pediatric urolithiasis occurs in 1% to 5% of children of developed nations,[52] although the incidence is higher in children with Down syndrome (ranging from 3 to 21.4%).[53,54]

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

According to the Saskatchewan Ministry of Health, the priority for renal scan for the evaluation of hydronephrosis is two to seven days, and eight to 30 days for GFR and ERFP measures for suspected urinary tract obstruction and impaired renal function (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). Prompt diagnosis is imperative, as an undiagnosed and untreated obstruction can result in significant morbidity including infection and permanent renal damage,[1,7,30]

Adult
Acute bilateral obstruction symptoms will disappear within hours or days if the disease is detected and treated promptly.[4] In chronic cases of obstruction, immediate interventions are not necessary except in cases where an infection needs to be drained or there is a solitary kidney.[27]

Pediatric
No pediatric-specific urgency classification for suspected obstructive uropathy was listed (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011); however, based on possible morbidities associated with a delay in diagnosis, the target time frame would be at a minimum similar to that of adults. UJO in children may resolve spontaneously within the first 18 months of life.[10,28]

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

According to Statistics Canada, 52 patients died from obstructive uropathy (1.6 per million people) and 39 due to urolithiasis (1.2 per million) in 2007 (ages not specified).[29] A 1999 study conducted by DeVivo et al. in patients with spinal cord injury reported that urinary complications accounted for 3.8% of deaths during the first year after injury and 2.3% of deaths beyond the first year after the injury has occurred.[55]

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

Adult

Renal obstruction for greater than one week may cause some permanent renal damage, but with recovery in renal function, while complete obstruction for greater than 12 weeks may cause irreversible damage to the renal system with no recovery of renal function.[7] In acute bilateral obstruction, symptoms will disappear within hours or days if the disease is detected and treated quickly. In chronic cases of obstruction, immediate interventions are not necessary, except in cases where an infection needs to be drained or the patient has one kidney.[27]

Cases of chronic obstruction may result in chronic tubulointerstitial disease[7] and can result in a decrease in renal blood flow,[7] glomerular filtration rate,[7,30] impaired renal function,[5,7,26] acidosis, and nephrogenic diabetes.[30] In acute unilateral obstruction, renal damage may occur, but it is rare, as the other kidney usually functions to compensate for the one that is impaired.[25]

Patients treated for obstruction or who clear a stone on their own may experience a life-threatening condition called post-obstructive diuresis,[26] which can be described as a loss of key electrolytes through the purged urine[7] after a blockage has been cleared.[26]

Pediatric

It is important to note that, in children, UJO may resolve spontaneously within the first 18 months of life. If symptoms persist past this time period, then intervention may be necessary.[10,28]

In pediatric cases, 23% of children with renal insufficiency will require transplantation.[30]

For both adults and children, complications associated with prolonged renal obstruction include long-term incontinence or urinary retention, and formation of urethral or kidney stones[26] and chronic/recurrent urinary tract infection (UTI).[5]

Return to Summary Table.

CRITERION 5: Relative impact on health disparities (link to definition)

Adult

Kidney stones occur in 2% to 12%of the population, but are twice as likely to occur in Caucasian populations compared to Asian populations.[48-52] The incidence of stone disease peaks between the ages of 20 through 50, and occurs more often in men than in women as a ratio of 3:1.[48]

Women who are pregnant[4] or have undergone female circumcision[56] may also be at a greater risk of developing urinary obstruction. However, renal scans would not be the procedure of choice in pregnant women because of the radiation (expert opinion — Martin Reed). Other populations that may be at a greater risk of developing urinary obstruction include individuals with prostate cancer,[2] retroperitoneal fibrosis,[7] spinal cord injury,[8,9] ureteral stricture,[6] and congenital anomalies (e.g., UJO),[5,10] which is most common in children but also found in adults.[6]

Pediatric

Children with Down's syndrome are more likely to have urinary obstruction (e.g., hydronephrosis [180 per 10,000 population], UJO [2.6 per 10,000 population], anterior urethral obstruction [2.6 per 10,000 population]) than children without Down's syndrome (obstruction of the urethra [0.3

per 10,000 children]).[54] However, nuclear imaging tests are not likely to be used in this patient population (expert opinion — Martin Reed).

Return to Summary Table.

CRITERION 6: Relative acceptability of the test to patients (link to definition)

Renal scintigraphy
Overall, renal scan is reported to be well-tolerated.[57] However, patients may have concerns about radiation exposure and the IV injection of a radiopharmaceutical agent. IV fluids might be required if the adequacy of hydration is a concern.[16] Because a full bladder may slow drainage of the radiopharmaceutical from the upper part of the urinary tract, the bladder should be emptied frequently. Bladder catheterization may be required, especially in pediatric patients. In particular in children, catheterization may be associated with some discomfort.[31]

MRU
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise. This may be less of a problem with new MRI machines, if available (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert opinion). It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[32,33] Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

U/S
This test may be preferred in pediatric patients, as there is no exposure to ionizing radiation and the test does not require sedation.

Return to Summary Table

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

Adult
No meta-analyses or systematic reviews with information regarding the diagnostic accuracy specific to an adult population was found; however, three primary studies[8,35,36] were identified that compared U/S, MRU, or CT to renal scans using ^{99m}Tc-MAG3 or ^{99m}Tc-DTPA. Only those studies that evaluated patients for an initial diagnosis of obstruction were included. Studies that evaluated obstruction after surgery or intervention for clearance of obstruction were not included. The main outcomes that were reported for diagnostic accuracy were the correlation coefficient of the renal scan compared with the alternative imaging test and, in some cases, sensitivity and specificity were reported (Appendix 4).

Results of the accuracy of diagnosis of hydronephrosis by renal scan and U/S are summarized in Table 2.

Renal scintigraphy versus MRU
Abou El-Ghar et al.[35] assessed the role of MRU and renal scintigraphy for the anatomical and functional evaluation of obstructed kidneys. A total of 96 patients (59 males, 37 female) with compromised renal function were included in the study (mean age = 52.5 ±14 years). All included patients underwent Gd-enhanced MRI and ^{99m}Tc-DTPA renal scan. Diagnosis of obstruction was confirmed by ureterogram or endoscopy and/or open surgery (gold standard). Anatomically, MRI detected the cause of the obstruction in all kidneys with non-calcular

obstruction (100% sensitivity) and in 21 kidneys with calcular obstruction (70% sensitivity). When combined with abdominal X-ray and ultrasonography, the sensitivity of MRI in detection of cause of obstruction was 97%. Functionally, a comparison between Gd-enhanced MRI and ^{99m}Tc-DTPA renal scan showed a good correlation ($r = 0.79$, $P < 0.0001$); the mean GFR value for the compromised kidneys was 14.6 ± 6 mL/min for the MRU and 18 ± 4.9ml min^{-1} for the renal scan. The authors concluded that the MRU is as accurate as renal scan in assessing renal function and could be used as a single modality for diagnosing obstruction in cases where patients would not be compromised due to renal function contraindications.[35]

El-Nahas et al.[36] evaluated the diagnostic accuracy of MRU in comparison with renal scan in 46 patients with pelvic-UJO (22 males, 24 females; mean age 31.6 years). All patients underwent ^{99m}Tc-MAG3 renal renography, while renal U/S or intravenous urography were also conducted for morphological changes. The clearance of the agents as assessed by both MRU and renal scan were calculated and compared using a correlation coefficient. The mean value of the MRU clearance was 32.8 mL/min, while the renal scan was 31.6 mL/min. The difference between the two tests was not statistically significant ($P = 0.19$); however, the correlation between the two values was ($r = 0.82$; $P < 0.001$). The authors concluded that there is a strong correlation between MRU and renal scan clearance, which can be attributed to the high accuracy of MRU in calculating renal clearance and diagnosing obstructive uropathy.[36]

Renal scintigraphy versus U/S

A 2001 study by Tsai et al.[8] evaluated the diagnostic accuracy of U/S and renal scan in the detection of hydronephrosis in patients with spinal cord injury (SCI) using intravenous pyelogram as the gold standard.[8] A total of 109 patients with SCI and hydronephrosis were evaluated over a three-year period from 1993 to 1996 at a rehabilitation hospital in Taiwan. The mean age of the group was 33.7 years and the main outcome measure was the ERPF using the radiopharmaceutical ^{99m}Tc-MAG3. Of analyzed kidneys, U/S correctly excluded the presence the hydronephrosis in 173 of 192 non-obstructed kidneys and positively identified 41 of 43 kidneys with documented hydronephrosis. The renal scan correctly excluded 161 non-obstructed kidneys and correctly identified 39 of 43 kidneys with hydronephrosis.[8] The corresponding sensitivity of U/S was 0.96, with a specificity of 0.91. Renal scan reached a sensitivity of 0.91 with a specificity of 0.84. The authors conclude that U/S was more accurate than renal scintigraphy for the detection of hydronephrosis in patients with SCI, although they add that renal scintigraphy can provide valuable information regarding total and individual renal function, which cannot be obtained by U/S alone.[8]

Table 2 presents a summary of diagnostic accuracy measures of imaging tests in adults with renal obstructive uropathy.

Table 2: Summary of Diagnostic Accuracy Measures of Tests in Adult Renal Obstructive Uropathy[8,35,36]

Test	Correlation Coefficient (R)*	Sensitivity (%)	Specificity (%)
MRU	0.79-0.82	70 to 100	N/A
U/S*	N/A	96	90

MRU = magnetic resonance urography; N/A= Not available; U/S = ultrasound.
*Between test and renal scan.

Pediatric

No meta-analyses or systematic reviews with information regarding the diagnostic accuracy specific to a pediatric population was found; however, five[12,14,18-20] primary studies were found that evaluated diagnostic accuracy of MRU and U/S in comparison with a radioisotope renal scan in a pediatric population of renal obstructive uropathy. Studies that included a population of children with renal obstructive uropathy that were diagnosed via U/S in the womb and were being evaluated after birth for a confirmation of diagnosis prior to surgical intervention were excluded.

Renal scintigraphy versus MRU

Jones et al.[14]

A study conducted by Jones and colleagues between November 2001 and September 2003 involved a total of 137 children in order to diagnose obstructive uropathy. MRU and renal scan with ^{99m}Tc DTPA (hence calculation of GFR) or ^{99m}Tc MAG3 (hence ERFP) were conducted on all the participants. The majority of the patient population involved boys (61%) with a mean age of 3.5 ± 4.5 years (range: 0.02 to 15.2 years) and girls (39%) with a mean age of 4.1±4.9 (range: 0.2 to 16.5). The renal transit time and split renal function were calculated as outcomes for the MRU to determine obstruction. Diagnosis of obstruction for renal scan was decided if the $T_{1/2}$ washout time was greater than 20 minutes after the administration of the diuretic. In final, data from 30 patients was included and a total of 59 kidneys evaluated. An receiver operating characteristic (roc) curve was generated, and the area under the curve (AUC) was calculated to be 0.90. This value means that the accuracy of MRU was 90% in comparison to renal scan as a gold standard (100%).[14]

Perez-Brayfield et al.[20]

Perez-Bayerfield and colleagues conducted a study to evaluate the role of dynamic enhanced MRI in order to compare it with other imaging modalities in the diagnosis of pediatric hydronephroisis. A total of 96 children (mean age four years) were involved in the study and a total of 100 dynamic contrast MRIs were done along with U/S and renal scan using ^{99m}Tc-MAG3 (n=71), ^{99m}Tc-DTPA (n=39) or ^{99m}Tc-DMSA (n=3). The SRF for nuclear imaging and MRI was compared in 71 of the 100 cases and the correlation coefficient was calculated to be r^2=0.93 which yields and r value of 0.96.

Grattan-Smith et al.[12]

Grattan-Smith and colleagues conducted a study to evaluate the role of dynamic enhanced MRI compared with other imaging modalities in the diagnosis of 40 children (mean age 1.4 years) with pediatric hydronephrosis. MRIs were done along with renal scan using ^{99m}Tc-MAG3 (n=22), ^{99m}Tc-DTPA (n=15) or ^{99m}Tc-DMSA (n=2). The SRF for renal scan and MRI was calculated and compared in all 40 cases. The correlation coefficient was calculated to be r=0.98. In conclusion, the authors summarized that in regards to the anatomical function, MRU was superior to renal scan, however, SRF outcomes between MRI and renal scan are equivalent.

Renal scintigraphy versus U/S

de Bessa Junior et al.[19]

A study conducted by de Bessa Junior et al. evaluated the diagnostic accuracy of U/S compared to renal scan to identify cases of urinary obstructions. A total of 54 patients were eligible for the study between September 2005 and October 2006; the median age of patients was four years (age range: 3 months to 14 years). All patients underwent U/S and renal scan using ^{99m}Tc-DTPA within a maximum of two weeks. For U/S, obstruction was diagnosed if the ureterovesical jet frequency was less than or equal to 25%. Renal scan was the reference test,

and obstruction was diagnosed as a measure of differential renal function less than 40%. The sensitivity and specificity for U/S in comparison to renal scan were calculated to be 87% (95% CI; 78.9% to 98.2%) and 96.4% (95% CI; 87% to 99%), respectively. The positive likelihood ratio and negative likelihood ratio were 24.3 and 0.1 respectively. The authors' conclude that a relative jet frequency value of less than or equal to 25% was a good indicator of obstructive uropathy and could be used as a non-invasive alternative to renal scan, but the authors state that further research is needed.[19]

Table 3: Summary of Diagnostic Accuracy Measures of the Tests in Pediatric Renal Obstructive Uropathy[12,14,18-20]

Test	Correlation Coefficient (R)*	Sensitivity (%),	Specificity (%)	Accuracy
MRU	0.96-0.98	N/A	N/A	0.90
U/S	N/A	87	96.4	N/A

CT = computed tomography; MRU = magnetic resonance urography; N/A= Not available; U/S = ultrasound
*Between test and renal scan.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Renal scan
Adverse events from renal scintigraphy are rare but may include reaction to the radiopharmaceutical, rash, fever, or chills.[37] There is also a relative contraindication in the administration of captopril in patients with a solitary kidney, as it may precipitate transient acute renal failure if the kidneys have physiologically significant renal artery stenosis (MIIMAC expert opinion).

MRU
MRI is contraindicated in patients with metallic implants including pacemakers.[58] MRI is often used in conjunction with the contrast agent Gd. Some patients may experience an allergic reaction to the contrast agent (if required), which may worsen with repeated exposure.[59] Side effects of Gd include headaches, nausea, and metallic taste. Gd is contraindicated in patients with renal failure or end-stage renal disease, as they are at risk of nephrogenic systemic fibrosis. According to the American College of Radiology *Manual on Contrast Media*[38] the frequency of severe, life-threatening reactions with Gd are extremely rare (0.001% to 0.01%). Moderate reactions resembling an allergic response (i.e., rash, hives, urticaria) are also very unusual and range in frequency from 0.004% to 0.7%.[38] Children may require sedation.

U/S
There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks
Among the modalities to diagnose obstructive uropathy, renal scintigraphy exposes the patient to ionizing radiation. The average effective dose of radiation delivered with each of these procedures can be found in Tables 4 and 5.

Table 4: Effective Radiation Doses for Various Imaging Tests in Adults

Test	Effective Radiation Dose (mSv)

Table 4: Effective Radiation Doses for Various Imaging Tests in Adults	
Test	**Effective Radiation Dose (mSv)**
^{99m}Tc-DTPA renal scan	1.8[44]
^{99m}Tc-MAG3 renal scan	2.6[44]
MRU	0
U/S	0
Average background dose of radiation per year	1-3.0[42-44]

MRU = magnetic resonance urography; mSv = millisievert; ^{99m}Tc-MAG3 = technetium-99m-labelled mercaptoacetyl triglycine; ^{99m}Tc-DTPA = technetium-99m-labelled- diethylenetriamine pentaacetic acid; U/S = ultrasound.

Table 5: Comparison of Radiation Exposure Levels of Different Imaging Tests in Pediatric Patients	
Diagnostic Study	**Average Radiation Dose (mSv)***
Renal scan with ^{99m}Tc-DMSA	0.039[39]
Renal scan with ^{99m}Tc-GH	0.024[60]
Renal scan with ^{99m}Tc-MAG3	0.015[39]
Renal scan with ^{99m}Tc-DTPA	0.012[39]
U/S	0[39]
MRI	0[39]
Average background dose of radiation per year	1-3.0[42-44]

MRI = magnetic resonance imaging; mSv = millisievert; ^{99m}Tc-MAG3 = technetium-99m-mercaptoacetyl triglycine; ^{99m}Tc-DTPA = technetium-99m-diethylenetriamine pentaacetic acid; ^{99m}Tc-GH = technetium-99m-glucoheptonate; ^{99m}Tc-MAG3 = technetium-99m-labelled mercaptoacetyltrigylcine; U/S = ultrasound.

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to evaluate suspected obstructive uropathy are presented by imaging modality. A summary of the availability of personnel required for renal scintigraphy or any of the alternative imaging modalities is provided in Table 6.

Renal scintigraphy

In Canada, physicians involved in the performance, supervision, and interpretation of renal scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging. Physicians should have a Fellowship of Certification in Nuclear Medicine or Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Nuclear medicine technologists are required to conduct renal scans. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities

In Canada, physicians involved in the performance, supervision, and interpretation of diagnostic MRI and U/S should be diagnostic radiologists[45] and must have a Fellowship or Certification in Diagnostic Radiology with the Royal College of Physicians and Surgeons of Canada and/or the Collège des médecins du Québec. Foreign-trained radiologists also are qualified if they are certified by a recognized certifying body and hold a valid provincial license.[61]

Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site.

Qualified medical physicists (on site or contracted-part time) should be available for the installation, testing, and ongoing quality control of MRI scanners and nuclear medicine equipment.[61]

MRU
MRU is an MRI-based test. For the performance of MRI, medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

U/S
Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[45] In Quebec, sonographers and medical radiation technologists are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[45]

Table 6: Medical Imaging Professionals in Canada[45]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	MRTs	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	–	–	NR	0
NT	0	0	26	1	NR	0
NU	0	0	–	–	NR	0
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; MRT = medical radiation technologist; ON = Ontario; NB = New Brunswick; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies within hospitals across Canada. Nuclear medicine cameras are not available in the Yukon, the Northwest Territories, and Nunavut. Table 7 provides an overview of the availability of equipment required to diagnose obstructive uropathy. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of MRI and SPECT/CT scanners is current to January 1, 2010. Data were not available for U/S.

Table 7: Diagnostic Imaging Equipment in Canada[45,46]

	Nuclear Medicine Cameras	MRI Scanners	SPECT/CT Scanners
Number of devices	603[45]	218[46]	96[46]
Average number of hours of operation per week (2006-2007)[45]	40	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	YT, NT, NU	PE, YT, NT, NU

MRI = magnetic resonance imaging; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; SPECT/CT = single-photon emission computed tomography/computed tomography; YT = Yukon.

Renal scintigraphy

For renal scans, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[45] In 2007, the latest year for which data are available, the average time for renal scintigraphy in McGill University Health Centre (MUHC) hospitals was 13 days. However, the wait times were reported to be less than one day for emergency cases.[62]

MRI

There are no MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[45] According to the Canadian Institute for Health Information's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in PEI to 99 hours in Ontario, with a national average of 71 hours.[45] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[47]

U/S

U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[47]

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of Lasix-enhanced renal scintigraphy and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 8), the cost of scintigraphy with ^{99m}Tc-based radioisotopes to establish whether obstruction is present is $310.45. U/S is a minimally less costly alternative. MRU is a moderately more costly imaging test.

Table 8: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[63]

Fee Code	Description	Tech. Fees ($)	Prof. Fees ($)	Total Costs ($)
Renal scintigraphy				
J835	Computer-assessed renal function — includes first transit	135.10	73.00	208.10
J880	Computer-assessed renal function — repeat after pharmacological intervention	46.00	22.50	68.50
Maintenance fees — from global budget		33.85		33.85
	TOTAL	214.95	95.50	**310.45**
MRU				
X451C	MRU — abdomen — multislice sequence		77.20	77.20
X455C ×3	Repeat (another plane, different pulse sequence; to a maximum of 3 repeats)		38.65 (×3) = 115.95	115.95
X487C	When Gd is used		38.60	38.60
X499C	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	373.00	297.15	**670.15**
U/S				
J135	Abdominal scan — complete	50.00	34.95	84.95
Maintenance fees — from global budget		3.30		3.30
	TOTAL	53.30	34.95	**88.25**

3-D = three-dimensional; Gd = gadolinium; MRI = magnetic resonance imaging; MRU = magnetic resonance urography; Prof. = professional; Tech. = technical; U/S = ultrasound.

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APPENDIX

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1948 to April 1, 2011>
Date of Search:	April 4, 2011
Alerts:	Weekly search updates began April 4, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	No date limit for systematic reviews; publication years 2001 – April 2011 for primary studies English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Ovid MEDLINE Strategy	
Line #	**Search Strategy**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	radioisotope*.mp.
6	(technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc* or 99mtechnetium* or 99m-technetium*).tw,nm.

Ovid MEDLINE Strategy	
7	Radionuclide Imaging/ or Perfusion Imaging/ or Radioisotope Renography/
8	ri.fs.
9	((radionucl* or nuclear or radiotracer* or perfusion or gamma camera*) adj2 (imag* or scan* or test* or diagnos*)).tw.
10	(SPECT or scintigraph* or scintigram* or scintiphotograph* or scintiscan*).tw.
11	Tomography, Emission-Computed, Single-Photon/
12	(single-photon adj2 emission*).tw.
13	((renal* or kidney* or dimercapto-succinic acid* or dimercaptosuccinic acid* or dimercapto-succinate acid* or dimercaptosuccinate acid*) adj7 (imaging or perfusion* or scan*)).tw.
14	(renograp* or reno-graph* or renogram* or DMSA).tw.
15	(MAG3 or MAG-3 or Mercaptoacetyltriglycine or Mertiatide or TechneScan or Mercaptoacetylglycylglycylglycine or Mercaptoacetyl triglycine).tw.
16	(DTPA or diethylenetriaminepentaacetic acid* or diethylenetriamine penta-acetic acid*).tw.
17	125224-05-7.rn.
18	or/1-17
19	Ureteral Obstruction/
20	exp Urethral Obstruction/
21	exp Hydronephrosis/
22	exp Urinary Calculi/
23	exp Renal Insufficiency/
24	((renal* or ureter* or urethra* or urinary*) adj3 (block* or obstruct*)).tw.
25	((fetal* or obstructi*) adj3 (uropath* or nephropath*)).tw.
26	(hydronephros* or calculus or calculi or (urinary adj2 stone*)).ti.
27	((kidney* or renal) adj3 (failure* or insufficienc*)).tw.
28	or/19-27
29	Meta-Analysis.pt.
30	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
31	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
32	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
33	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
34	(data synthes* or data extraction* or data abstraction*).tw.
35	(handsearch* or hand search*).tw.
36	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin

Ovid MEDLINE Strategy	
	square*).tw.
37	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).tw.
38	(meta regression* or metaregression* or mega regression*).tw.
39	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
40	(medline or Cochrane or pubmed or medlars).tw,hw.
41	(cochrane or health technology assessment or evidence report).jw.
42	or/29-41
43	exp "Sensitivity and Specificity"/
44	False Positive Reactions/
45	False Negative Reactions/
46	du.fs.
47	sensitivit*.tw.
48	(predictive adj4 value*).tw.
49	distinguish*.tw.
50	differentiat*.tw.
51	enhancement.tw.
52	identif*.tw.
53	detect*.tw.
54	diagnos*.tw.
55	accura*.tw.
56	comparison*.tw.
57	Comparative Study.pt.
58	(Validation Studies or Evaluation Studies).pt.
59	Randomized Controlled Trial.pt.
60	Controlled Clinical Trial.pt.
61	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
62	Multicenter Study.pt.
63	(random* or sham or placebo*).ti.
64	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
65	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
66	(control* adj3 (study or studies or trial*)).ti.
67	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
68	(allocated adj "to").ti.
69	Cohort Studies/

Ovid MEDLINE Strategy	
70	Longitudinal Studies/
71	Prospective Studies/
72	Follow-Up Studies/
73	Retrospective Studies/
74	Case-Control Studies/
75	Cross-Sectional Study/
76	(observational adj3 (study or studies or design or analysis or analyses)).ti.
77	cohort.ti.
78	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
79	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
80	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
81	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
82	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
83	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
84	(population adj3 (study or studies or analysis or analyses)).ti.
85	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
86	or/43-85
87	Case Reports.pt.
88	86 not 87
89	18 and 28 and 42
90	limit 89 to english language
91	or/19-22,24-26
92	18 and 91 and 88
93	limit 92 to (english language and humans and yr="2001 -Current")

OTHER DATABASES
Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCH	
Dates for Search:	April 2011
Keywords:	Included terms for radionuclide imaging and obstructive uropathy.
Limits:	No limits

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (CADTH Grey Matters checklist) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search

Appendix 3: Definitions

Area under the curve (AUC): The area under the receiver operating characteristic (ROC) curve (AUC) is widely recognized as the measure of a diagnostic test's discriminatory power. The maximum value for the AUC is 1.0, thereby indicating a (theoretically) perfect test (i.e., 100% sensitive and 100% specific)[64]

Calculi: Is the plural of calculus, commonly called stone. A calculus is usually composed of mineral salts. These pathological concretions can occur in the kidneys, ureters, bladder, and urethra, and are usually formed of crystalling urinary salts held together by viscous organic matter.[23]

Calyces: Plural of calyx. A cuplike part of the urinary collecting portion of the kidney. The calyx is the method by which urine is passed from the kidney to the bladder.[65]

Differential Renal function: See SRF.

Diuretic: An agent that increases the secretion of urine.[23]

Effective renal plasma flow (ERPF): The rate at which the radioisotope is cleared by the proximal tubules, with only a small fraction cleared by the glomerulus tubules. In individuals with healthy kidneys, this clearance rate is 500 to 600 mL/min. This measure can be calculated by examining the uptake and clearance rate of a radioisotope to determine renal function.[16]

Glomerular filtration rate (GFR): The rate at which the radioisotope clears the glomerulus tubules of the kidney.[16]

Hydronephrosis: The swelling of the kidneys[5] or top of the ureter,[10] which can be due to an obstruction in the urinary tract.[5]

Nephrolithiasis: The presence of calculi in the kidney.[23]

Pyelocaliectasis: Dilation of the pelvis and cavities (calyces) of the kidney.[23]

Receiver operating characteristic (roc): The ROC curve offers a graphical illustration of these trade-offs at each "cut-off" for any diagnostic test that uses a continuous variable. Ideally, the best "cut-off" value provides both the highest sensitivity and the highest specificity, easily located on the ROC curve by finding the highest point on the vertical axis and the furthest to the left on the horizontal axis (upper-left corner).[64]

Renal transit time (RTT): The time it takes for the contrast material to move from the kidneys to the level of or below the lower pole of the kidney (ureter).[14]

Resistive Index (RI): A measure of (peak systolic velocity – peak diastolic velocity)/peak systolic velocity.

Split renal function (SRF) OR differential renal function (DRF) OR differential ureteral catherization test: Compares the areas of two kidneys; can be calculated by the accumulation of the radiotracer in the kidney after injection.[19] It is used to determine various function parameters of one kidney compared with the other kidney.

Tetany: A nervous affection characterized by intermittent tonic spasms.[23]

Ureterolithiasis: Development of a calculus in the ureter.[23]

Ureterovesical jets (urinary jet): A wavelike (peristaltic)[23] inflow into the bladder.[19]

Ureterolpelvic Junction Obstruction(UJO): A congenital anomaly prevalent in children that causes an obstruction where the ureter joins the pelvis.[10]

Urolithiasis: Formation of urinary calculi and the illness associated with the presence of urinary calculi in the urinary tract.[23]

Washout half-time ($T_{1/2}$): The time it takes for 50% of the radioisotope to exit the kidneys after the injection of the diuretic (e.g., furosemide or LASIX).[18,19] A diagnosis of obstruction is considered when $T_{1/2}$ > 20 minutes to 30 minutes.[18]

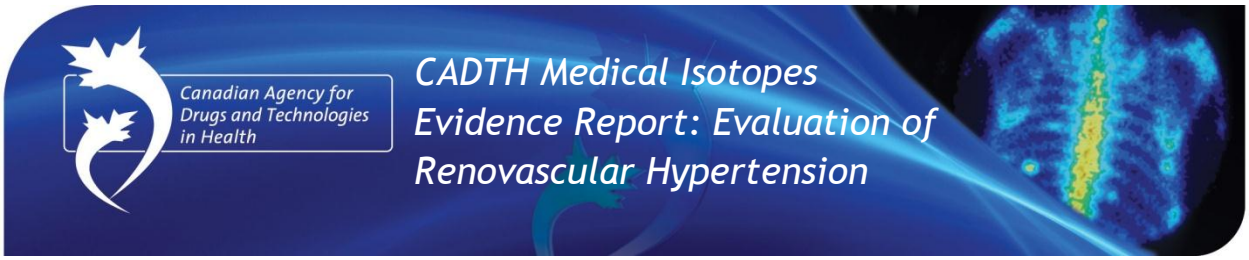
Appendix 4: Diagnostic Accuracy

Table 9: Diagnostic Accuracy of Renal Scan and the Alternative Tests Based on the Information Presented in the Included Studies						
Study	**Population Size, *Outcome Measured, and* (Mean Age)**	**Renal Scan ^{99m}Tc**	**X-ray**	**U/S**	**MRU**	**CT**
Adult						
Tsai et al., 2001[8]	109 patients with SCI, *ERPF,* (33.7 years)	Sens: 91% Spec: 84% PPV: 56% NPV: 98%	Reference standard	N/A	*N/A*	N/A
El-Ghar et al., 2008[35]	96 adults unilateral, bilateral chronic obstructive hydronephrosis and compromised renal function, *GFR* (52.5 years)	Mean: 18 ± 4.9mL/ min^{-1} R= see MRU	N/A	N/A	Mean 14.6 ± 6ml min^{-1} R = 0.79	N/A
El-Nahas et al., 2007[36]	46 patients with symptomatic pelvic UJO, *GFR* (31.6 years)	Mean: R = see MRU	N/A	N/A	Mean R = 0.82	N/A
Pediatric						
de Bessa Jr. et al., 2007[19]	54 pediatric patients *Renal scan: $T_{1/2}$* *U/S : RJF* (4 years)	Reference standard	N/A	Sens 87% Spec 96.4 PLR 24.3 NLR 0.1	N/A	N/A
Jones et al., 2004[14]	126 pediatric patients *SRF* (4.1 years)	Reference standard	N/A	N/A	AUC : 0.90 Acc: 90%	N/A
Perez-Brayfield	96 pediatric patients	R = see MRU	N/A	N/A	R = 0.96	N/A

Table 9: Diagnostic Accuracy of Renal Scan and the Alternative Tests Based on the Information Presented in the Included Studies						
Study	**Population Size, *Outcome Measured, and* (Mean Age)**	**Renal Scan ^{99m}Tc**	**X-ray**	**U/S**	**MRU**	**CT**
et al., 2003[20]	*SRF* (4 years)					
Grattan-Smith et al., 2003[12]	40 pediatric patients *SRF* (1.4 years)	R = see MRU	N/A	N/A	R = 0.98	N/A

AUC=area under the curve; CT= computed tomography; ERFP = effective renal plasma flow; GFR = glomerular filtration rate; MRU= magnetic resonance urography; NA = not applicable; NLR= negative likelihood ratio; NPV= negative predictive value; PLR=positive likelihood ratio; PPV=positive predictive value, R= correlation coefficient; RJF = renal jet frequency; Sens= sensitivity; Spec= specificity; SRF = split renal function; ^{99m}Tc = technetium-99m;UJO = ureteropelvic junction obstruction; U/S = ultrasound.

APPENDIX 2.18



INDICATION OVERVIEW

Cause of high blood pressure is unknown in about 90% of patients with hypertension (i.e., idiopathic hypertension). In approximately 10% of cases, a cause such as renal hypertension can be identified and, in many cases, a specific treatment may be available. Renal hypertension refers to high blood pressure related to renal artery stenosis (RAS). RAS is the narrowing of one or more renal arteries which supply blood to the kidneys. When the renal arteries are narrowed, the kidneys receive less blood flow and respond as though an individuals' blood pressure is too low.[1] Hormones are released which cause blood vessels to constrict and the body to retain sodium and water. The constriction of blood vessels and the retention of water lead to hypertension (high blood pressure). RAS is usually caused by hardening of the renal arteries due to plaque build-up from cholesterol (atherosclerosis).[2] Another cause of renal artery stenosis is fibromuscular dysplasia.

There are a number of clinical factors that can lead to suspicion of renal hypertension. These include hypertension that remains uncontrolled following the use of three or more hypertensive medications, sudden onset or sudden worsening of uncontrolled hypertension, malignant hypertension, and unexplained azotemia (higher than normal levels of urea or other nitrogen compounds in the blood). It is important to properly diagnose renal hypertension in order for treatment to be initiated.[3] Treatment for renal hypertension includes pharmaceutical therapy, angioplasty of the narrowed renal arteries, with or without stent, and surgical revision of renal artery stenosis.[4]

Population: Patients with suspected renal hypertension.

Intervention: Renal scintigraphy.

Renal scintigraphy refers to nuclear medicine imaging of the kidneys. For the diagnosis of renal hypertension, renal scintigraphy is augmented by the use of an angiotensin-converting enzyme (ACE) inhibitor, usually captopril. The following illustrates why we use ACE inhibitors in renovascular hypertension renal scintigraphy. When blood flow to the kidneys is reduced due to renal artery stenosis, the kidney releases renin, a hormone responsible for the activation of ACE, which converts angiotensin I to angiotensin II. Angiotensin II promotes increased blood pressure in a number of ways including: increased water retention (i.e., increased pituitary antidiuretic hormone secretion); increased sodium retention (i.e., increased adrenal aldosterone secretion); and, widespread vasoconstriction (i.e., specifically arteriolar).

In captopril renal scintigraphy, patients are administered the ACE inhibitor prior to being injected with a radiopharmaceutical. Radiopharmaceuticals used in renal captopril scintigraphy include technetium-99m-labelled-diethylenetriamine pentaacetic acid (^{99m}Tc-DTPA), technetium-99m-labelled mercaptoacetyl trigylcine (^{99m}Tc-MAG3) and, historically, ^{123}I-orthoiodohippurate (^{123}I-OIH).[5] Captopril inhibits the conversion of angiotensin I to angiotensin II and therefore causes blood vessels to become less constricted, including those vessels in the kidneys which, in the presence of RAS, constrict to maintain adequate renal blood flow and function. In patients with RAS, ACE inhibitors cause a temporary change in renal function[2,6] including decreased glomerular filtration and maintained effective renal plasma flow (ERPF). These changes in renal

function can be measured over time based on the uptake pattern of the injected radiopharmaceutical in the kidneys.

Uptake of the radiopharmaceutical is measured using multiple images taken with a gamma camera over time. Results from captopril renal scintigraphy are compared to results from a baseline renal scintigraphy taken without captopril. Compared to baseline measurements, captopril renal scintigraphy shows a decrease in glomerular filtration (i.e., ^{99m}Tc-DTPA studies) or progressive renal cortical retention (i.e., ^{99m}Tc-MAG3) in patients who have significant renal artery stenosis.[2]

Comparators: For this report, the following diagnostic tests are considered as alternatives to renal scintigraphy:

- *Catheter angiography:* During catheter angiography patients are placed on an X-ray table; a catheter is inserted through the skin, with the help of a needle and wire, and is pushed into the aorta. A contrast dye is injected through the catheter into the kidney artery in order to better visualize it. After the injection of contrast dye, X-ray images of the artery are taken,[7] which show where an artery may be blocked or narrowed. The degree of the blockage can be measured. A blockage of at least 50% is often considered clinically significant.[7] Bones and tissues around the kidney may be "subtracted" out by a computer, which allows for only the blood vessels with contrast dye in them to be visible. An angiogram that includes subtraction is referred to as digital subtraction angiography (DSA).[7]

- *Computed tomography angiography (CTA):* A CTA scan is a computed tomography (CT) scan that visualizes blood vessels in the body. Images are taken with a rotating X-ray device that moves around the patient and takes multiple detailed images of the blood vessels being investigated. Patients are injected with a contrast dye before images are taken in order to better visualize the blood vessels.

- *Magnetic resonance angiography (MRA)*: An MRA is a magnetic resonance imaging (MRI) test that captures detailed images of the body's blood vessels, which include the renal arteries.[6] Patients undergoing MRA are placed onto a table that is moved into the centre of the MRI machine. Patients are often given contrast material before the MRA is undertaken to help visualize the blood vessels.

- *Ultrasound (U/S):* During a U/S, a transducer is placed over the organ of interest. The transducer produces sound waves that pass through the body, producing echoes which are analyzed by a computer to develop images of the body part being analyzed.[8] Using Doppler U/S, the diagnosis of renal artery stenosis is based upon changes in blood flow velocity across the length of the renal artery.[6]

Outcomes: Eleven outcomes (referred to as criteria) are considered in this report:

- Criterion 1: Size of the affected population
- Criterion 2 : Timeliness and urgency of test results in planning patient management
- Criterion 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition
- Criterion 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition
- Criterion 5: Relative impact on health disparities

- Criterion 6: Relative acceptability of the test to patients
- Criterion 7: Relative diagnostic accuracy of the test
- Criterion 8: Relative risks associated with the test
- Criterion 9: Relative availability of personnel with expertise and experience required for the test
- Criterion 10: Accessibility of alternative tests (equipment and wait times)
- Criterion 11: Relative cost of the test.

Definitions of the criteria are in Appendix 1.

METHODS

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE with In-Process records via Ovid; The Cochrane Library (2011, Issue 1) via Wiley; PubMed; and University of York Centre for Reviews and Dissemination (CRD) databases. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were radionuclide imaging and renal hypertension.

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses (HTA/SR/MA), randomized controlled trials, non-randomized studies, and diagnostic accuracy studies. No date or human limits were applied to the HTA/SR/MA search. For primary studies, the retrieval was limited to documents published between January 1, 2001 and April 5, 2011, and the human population. Both searches were also limited to English language documents. Regular alerts were established to update the search until October 2011. Detailed search strategies are located in Appendix 2.

Grey literature (literature that is not commercially published) was identified by searching relevant sections of the CADTH Grey Matters checklist. Google was used to search for additional web-based materials. The searches were supplemented by reviewing the bibliographies of key papers. See Appendix 2 for more information on the grey literature search strategy.

Targeted searches were done as required for the criteria, using the aforementioned databases and Internet search engines. When no literature was identified addressing specific criteria, experts were consulted.

SEARCH RESULTS

There were 22 articles identified through the MA/SR/HTA search. Of those, 11[5,9-18] underwent full-text review. One systematic review[12] was identified from the full-text review that compared the diagnostic accuracy of renal scintigraphy with the alternative imaging modalities (U/S, CTA, MRA, catheter angiography).

The systematic review was published in 2001 and included studies published up to August 2000. For the current report, a search for primary studies evaluating renal scintigraphy, and at a least one of its alternatives (U/S, CTA, MRA, catheter angiography), published after 2000, was conducted. Seven primary studies were included: six comparing renal scintigraphy to catheter angiography,[19-24] two comparing renal scintigraphy to CTA,[21,25] two comparing renal scintigraphy to MRA,[21,25] and three comparing renal scintigraphy to U/S.[20,21,25]

One article from the primary study search was used to help address criterion #1.[26] Literature from targeted searches was used to supplement the articles identified in the primary and grey literature searches for the remaining criteria.

SUMMARY TABLE

Table 1: Summary of Criterion Evidence		
Domain 1: Criteria related to the Underlying Health Condition		
Criterion		**Synthesized Information**
1	**Size of the affected population**	RAS has been identified as the primary cause of hypertension in 1% to 5% of individuals. Using 1% as an estimate, the prevalence of renal hypertension in Canada can be estimated to be 2.21 per 1,000 people (0.22%). Therefore, the size of the affected population is more than 1 in 1,000 (0.1%) and less than or equal to 1 in 100 (1%).
2	**Timeliness and urgency of test results in planning patient management**	According to the urgency classifications developed by the province of Saskatchewan, it is recommended that renal scintigraphy for hypertension with suspected renal artery stenosis be conducted within eight to 30 days from the time and date the request for an examination is received by the imaging department, to the date the examination is performed. (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011). Imaging has minimal impact on the management of the condition or the effective use of heath care resources.
3	**Impact of not performing a diagnostic imaging test on mortality related to the underlying condition**	No studies assessing the impact of diagnostic imaging tests on the mortality of individuals with renovascular hypertension were identified. If an imaging test for diagnosing renal hypertension is not available, patients may not receive appropriate treatment to deal with the underlying condition causing their hypertension. Hypertension can lead to conditions with large impacts on mortality including myocardial infarction, stroke, congestive heart failure, and renal failure. Diagnostic imaging test results are assumed to have a minimal impact on mortality.
4	**Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition**	Correct diagnosis and subsequent appropriate treatment of renal hypertension may reduce the risk of developing conditions linked to hypertension including myocardial infarction, stroke, congestive heart failure, and renal failure, all of which may contribute to morbidity and reduced QoL. Diagnostic imaging test results are assumed to have a minimal impact on morbidity or QoL.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
5	**Relative impact on health disparities**	To be scored locally.
6	**Relative acceptability of the test to patients**	*Renal scintigraphy:* Patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. *Catheter angiography:* Patients may have concerns about radiation exposure and injection of a contrast agent. The catheter is inserted through the groin, with the help of a needle and wire, and is pushed into the aorta. *CTA:* Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner (MIIMAC expert opinion). They may also have concerns about reactions to the CT contrast agent, and in the case of reduced renal function, of further renal impairment (MIIMAC expert opinion). *MRA:* MRA is an MRI-based technique. Patients undergoing MRI are susceptible to anxiety, during and after the test.[27,28] Up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[27] Approximately 90% of patients would be willing to undergo an MRI exam again.[29,30] *U/S:* Overall, patients are satisfied with U/S. Renal scintigraphy using ^{99m}Tc-radiolabelled isotopes: • is significantly more acceptable than catheter angiography • is moderately more acceptable than CTA • is minimally less acceptable than MRA • is minimally less acceptable than U/S.
7	**Relative diagnostic accuracy of the test**	One meta-analysis from 2001[12] and one primary study[21] compared the diagnostic accuracy of renal scintigraphy to all of its alternatives. Another primary study[25] compared the diagnostic accuracy of renal scintigraphy to all of its alternatives except for catheter angiography.

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses

Criterion	Synthesized Information

Meta-analysis of Diagnostic Accuracy of Tests for Renovascular Hypertension[12]

Test	Diagnostic Accuracy
Renal scintigraphy	0.92
Catheter angiography	Reference
CTA	0.99
MRA	0.99
U/S	0.93

CTA = computed tomography angiography; MRA = magnetic resonance angiography; U/S = ultrasound.

Primary Studies of Diagnostic Accuracy of Tests for Renovascular Hypertension[21,25]

Test	Eklof et al.[21]		Eriksson et al.[25]	
	Sensitivity	Specificity	Sensitivity	Specificity
Renal scintigraphy	0.59	0.50	0.42	1.00
Catheter angiography	0.95	0.91	NR	NR
CTA	1.00	0.56	Reference test	
MRA	0.98	0.70	0.81	0.79
U/S	0.80	0.54	0.70	0.89

CTA = computed tomography angiography; MRA = magnetic resonance angiography; NR = not reported; U/S = ultrasound.

Based on the available evidence, the diagnostic accuracy of renal scintigraphy using ^{99m}Tc-radiolabelled isotopes is:

- minimally lower than catheter angiography
- similar to CTA
- similar to MRA
- similar to U/S.

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td>8</td><td>Relative risks associated with the test</td><td>
Non-radiation-related Risks

Renal scintigraphy: AEs from renal scintigraphy are rare but may include allergy to the radiopharmaceutical, rash, fever, or chills.[31] There is also a relative contraindication in the administration of captopril in patients with a solitary kidney, as it may precipitate transient acute renal failure if kidneys have physiologically significant renal artery stenosis (MIIMAC expert opinion).

Catheter angiography: Risks of catheter angiography include side effects from contrast dye that is used during the procedure, arterial occlusion, and damage to the artery or artery wall, which can lead to blood clots.[7]

CTA: Patients may experience side effects from contrast dye. A recent large retrospective study found that 0.15% of patients given CT contrast material experienced side effects, most of which were mild.[32] The percentage of patients experiencing a serious side effect (defined as cardiovascular collapse, moderate or severe bronchospasm, laryngeal edema, loss of consciousness, or seizure) was 0.005%.[32]

MRA: MRA (which uses an MRI machine) does not expose patients to any radiation.[33] The toxicity of the MRA contrast agent Gd is of particular concern for patients with renal failure. In such patients, Gd has been linked to nephrogenic fibrosis — a serious disease affecting the skin, internal organs, and muscles.[32,34]

U/S: U/S does not expose patients to any radiation.[33] There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

<table>
<tr><th colspan="2">Effective Doses of Radiation Associated with Diagnostic Tests</th></tr>
<tr><th>Test</th><th>Effective Radiation Dose (mSv)[35]</th></tr>
<tr><td>Renal scintigraphy with ^{99m}Tc-DTPA</td><td>1.8</td></tr>
<tr><td>Renal scintigraphy with ^{99m}Tc-MAG3</td><td>2.6</td></tr>
<tr><td>Catheter angiography</td><td>2.6</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th colspan="3">Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>
<table>
<tr><td>CTA</td><td>8.0</td></tr>
<tr><td>MRA</td><td>0</td></tr>
<tr><td>U/S</td><td>0</td></tr>
<tr><td>Average background dose of radiation per year</td><td>1 to 3.0[35-37]</td></tr>
</table>
CTA = computed tomography angiography; MRA = magnetic resonance angiography; mSv = millisievert; ^{99m}Tc-DTPA = technetium-99m diethylenetriamine pentaacetic acid; ^{99m}Tc- MAG3 = ^{99m}Tc- technetium-99m mercaptoacetyl triglycine; U/S = ultrasound.

Overall, renal scintigraphy using ^{99m}Tc-radiolabelled isotopes is:

significantly safer than catheter angiography
moderately safer than CTA
minimally safer than MRA
minimally less safe than U/S.

</td></tr>
<tr><td>9</td><td>Relative availability of personnel with expertise and experience required for the test</td><td>
Renal scintigraphy: Requires nuclear medicine physicians or diagnostic radiologists with training in nuclear imaging. Nuclear medicine technologists are also required to conduct renal scans.

Catheter angiography: Catheter angiography is an X-ray based test performed by diagnostic radiologists with a thorough understanding of vascular anatomy, angiographic equipment, and radiation safety considerations.[7]

CTA: For the performance of CT scan, medical radiation technologists who are certified by CAMRT, or an equivalent licensing body recognized by CAMRT, are required. The training of technologists
</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses		
Criterion		**Synthesized Information**
		specifically engaged in CT should meet with the applicable and valid national and provincial specialty qualifications. *MRA:* MRA is an MRI-based test. For the performance of MRI, medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT. *U/S*: Sonographers should be graduates of an accredited school of sonography or have obtained certification by the CARDUP. They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[38] In Quebec, sonographers and MRTs are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[38] Assuming the necessary equipment is available, if ^{99m}Tc imaging using renal scintigraphy is not available, it is estimated that: • 25% to 74% of the procedures can be performed in a timely manner using catheter angiography • more than 95% of the procedures can be performed in a timely manner using CTCA • 25% to 74% of the procedures can be performed in a timely manner using MRA • 25% to 74% of the procedures can be performed in a timely manner using U/S.
10	**Accessibility of alternative tests (equipment and wait times)**	*Catheter angiography* Based on the experiences of hospitals in a large Canadian city, the average wait time for an elective angiography procedure was 21 days.[39] Renal catheter angiography requires the use of an angiography suite. As of 2007, there were 179 angiography suites available in Canada. This is equivalent to 5.5 angiography suites per one million people.[38] *CTA* No CT scanners are available in Nunavut.[40] The average weekly use of CT scanners ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[38] In 2010, the average wait time for a CT scan in Canada was 4.2 weeks.[41] *MRA* There are no MRI scanners available in the Yukon, Northwest Territories, or Nunavut.[40] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of

<table>
<tr><th colspan="3">**Domain 2:** Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses</th></tr>
<tr><th colspan="2">Criterion</th><th>Synthesized Information</th></tr>
<tr><td></td><td></td><td>hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario, with a national average of 71 hours.[38] In 2010, the average wait time for MRI in Canada was 9.8 weeks.[41]

U/S

The average wait time for a U/S in Canada was estimated to be 4.5 weeks in 2010.[41] No information was found on the number of U/S machines available in Canada.

Assuming the necessary expertise is available, if ^{99m}Tc imaging using renal scintigraphy is not available it is estimated that:

• 25% to 74% of the procedures can be performed in a timely manner using catheter angiography
• more than 95% of the procedures can be performed in a timely manner using CTA
• 25% to 74% of the procedures can be performed in a timely manner using MRA
• more than 95% of the procedures can be performed in a timely manner using U/S.</td></tr>
<tr><td>11</td><td>Relative cost of the test</td><td>According to our estimates, the cost of scintigraphy with ^{99m}Tc-based radioisotopes is $327.38. There is essentially no difference between the cost of renal scintigraphy and the cost of CT. MRA and RCA are moderately more costly tests. U/S is a minimally less costly alternative.

<table>
<tr><th colspan="3">Relative Costs</th></tr>
<tr><th>Test</th><th>Total Costs ($)</th><th>Cost of Test Relative to ^{99m}Tc-based Test ($)</th></tr>
<tr><td>Renal scintigraphy</td><td>327.38</td><td>Reference</td></tr>
<tr><td>CT</td><td>306.82</td><td>-20.56</td></tr>
</table>
</td></tr>
</table>

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative or Comparing Between Clinical Uses				
Criterion		**Synthesized Information**		
		MRA	670.15	+342.77
		RCA	717.96	+390.58
		U/S	88.25	-239.13

AE = adverse event; CAMRT = Canadian Association of Medical Radiation Technologists; CIHI = Canadian Institute for Health Information; CT = computed tomography; CTA = computed tomographic angiography; Gd = gadolinium; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MRT = medical radiation technologist; mSv = millisievert; NR = not reported; QoL = quality of life; RAS = renal artery stenosis; RCA = renal catheter angiography; ^{99m}Tc-DTPA = technetium-99m-diethylenetriamine pentaacetic acid; ^{99m}Tc-MAG3 = technetium-99m mercaptoacetyl triglycine; U/S = ultrasound.

CRITERION 1: Size of affected population (link to definition)

No estimates of point prevalence of renal hypertension in Canada were found in the literature. However, two recent Canadian-based studies that estimated the prevalence and incidence of hypertension were identified.[42,43]

Tu et al.[42] estimated the number of adults with hypertension in Ontario based on physician billing claims from the Ontario Health Insurance Plan (OHIP) database and hospital discharge data from the Canadian Institute of Health Information (CIHI) database. Individuals were considered to have hypertension if they had two physician billing codes or one hospital discharge with a diagnosis of hypertension within a two-year period. The prevalence of hypertension in 2005 was estimated to be 244.8 per 1,000 people. The annual incidence of physician-diagnosed hypertension was estimated to be 32.1 per 1,000 patients.

The prevalence of hypertension across Canada was estimated using the Canadian Chronic Disease Surveillance System (CCDSS)[43] — a network of provincial and territorial surveillance systems. For each province, health insurance, physician billing, and hospitalization databases are linked together. Similar to the assumptions made in Tu et al.,[42] individuals were considered to have hypertension if they had two physician billing codes or one hospital discharge with a diagnosis of hypertension within a two-year period. As of 2006–2007, the overall prevalence of hypertension in Canada was estimated to be 196 per 1,000 people.

Renal artery stenosis has been identified as the primary cause of hypertension in 1% to 5% of individuals.[26] If 1% of all hypertension is due to renal artery disease and the prevalence of all hypertension in Canada is 221 per 1,000 people, the prevalence of renal hypertension can be estimated as 2.21 per 1,000 population (11.1 = 221 × 1%).

Return to Summary Table.

CRITERION 2: Timeliness and urgency of test results in planning patient management (link to definition)

Saskatchewan hospital guidelines recommend that renal scintigraphy for hypertension with suspected renal artery stenosis be conducted within eight to 30 days of symptom onset (Patrick Au, Acute and Emergency Services Branch, Saskatchewan Ministry of Health: unpublished data, 2011).

Return to Summary Table.

CRITERION 3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition (link to definition)

If a test for diagnosing renal hypertension (i.e., renal scintigraphy or relevant comparators) were not available, patients may not receive appropriate treatment to deal with the underlying condition causing their hypertension. Hypertension can lead to conditions with large impacts on mortality including myocardial infarction, stroke, congestive heart failure, and renal failure.

No studies were identified that assessed the mortality impact of renal hypertension. However, one Canadian-based study was found that measured the mortality impact of hypertension in general.[43] Individuals diagnosed with hypertension were identified using the CDSS. The CDSS reported that, in fiscal 2006–2007, the all-cause mortality for adult women (20 years of age or

older) with and with without hypertension in Canada was 6.7 per 1,000 and 5.0 per 1,000, respectively. For men, these numbers were reported to be 10.2 per 1,000 and 7.1 per 1,000. Based on this data, the relative risk of mortality for women and men with hypertension can be estimated to be 1.34 and 1.44, respectively.

Return to Summary Table.

CRITERION 4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition (link to definition)

If a test for diagnosing renal hypertension is not available, appropriate treatment may not be provided. Though hypertension itself is usually non-symptomatic, it is linked with increased risk of events such as myocardial infarction, stroke, congestive heart failure, and renal failure, which significantly impact quality of life (QoL). Correct diagnosis and subsequent appropriate treatment of renal hypertension may reduce the risk of developing these conditions.

The QoL impact of hypertension was assessed in a systematic review (SR) and meta-analysis (MA) by Trevisol et al.[44] published in 2011. The authors reviewed studies that assessed health-related QoL associated with hypertension, measured using the generic health status questionnaires Short Form 36 (SF-36) or Short Form 12 (SF-12). The SF-36 instrument contains eight domains: physical function, role-physical, bodily pain, general health, vitality, social function, role-emotional, mental health; and two summary scores: physical component score (PCS) and mental component score (MCS). Scores are all standardized and range from zero to 100, with higher scores indicating better QoL. The SF-12 is a shorter version of SF-36; performance is comparable to that of SF-36, with the advantage of it being easier and quicker to complete.[45] Six of the 20 articles included in the SR (published between January 1980 and August 2009) presented scores of QoL in all domains and were therefore included in the MA.

Selected results from the MA are provided in Table 2. Trevisol et al.[44] found hypertensive patients to have a lower PCS and MCS compared to individuals without hypertension. The differences in the PCS and MCS scores for hypertensive individuals was estimated to be –2.4 (95% confidence interval [CI], –4.8 to –0.1) and –1.7 (95% CI, –2.1 to –1.2), respectively. For all individual domains, pooled scores were lower for hypertensive patients compared to non-hypertensive individuals.

It is difficult to conclude whether the lower QoL for hypertensive patients is due to the QoL impact of health conditions caused by hypertension or by other factors. The authors discussed that the lower of QoL may be due to patients simply being aware that they have hypertension. Another factor may be side effects from antihypertensive medications.

Table 2: Selected Results Reported in Trevisol et al.[44]

Component Scores	Mean Difference (95% Confidence Interval)
Physical Component Score	–2.4 (–4.8 to –0.1)
Mental Component Score	–1.7 (–2.1 to –1.2)
Domain Scores	
Physical Functioning	–8.3 (–12.9 to –3.7)
Bodily Pain	–5.9 (–9.6 to –2.3)
Vitality	–4.2 (–6.7 to –1.7)
Role-Emotional	–4.4 (–8.3 to –0.4)
Role-Physical	–8.1 (–14.0 to –3.7)

Table 2: Selected Results Reported in Trevisol et al.[44]	
General Health	–8.9 (–13.1 to –4.8)
Social Functioning	–3.7 (–5.9 to –1.5)
Mental Health	–2.7 (–4.3 to –1.1)

Return to Summary Table.

CRITERION 5: Relative impact on health disparities (link to definition)

To be scored locally.

No information was found on the potential health disparity for alternative imaging tests.

Return to Summary Table.

CRITERION 6: Relative acceptability of the test to patients (link to definition)

Renal scintigraphy
Overall, renal scan is reported to be well-tolerated.[46] However, patients may have concerns about radiation exposure and the intravenous injection of a radiopharmaceutical agent. Intravenous fluids might be required if the adequacy of hydration is a concern.[47] Because a full bladder may slow drainage of the radiopharmaceutical from the upper part of the urinary tract, the bladder should be emptied frequently.

Catheter angiography
Catheter angiography is a relatively invasive test. Patients are placed on a table and a catheter is inserted through the groin, with the help of a needle and wire, and is pushed into the aorta.[7]

CTA
Patients undergoing CT scan may have concerns about radiation exposure and may also feel claustrophobic while in the scanner; however, this may be less of a problem with new CT scanners, if available (Medical Isotopes and Imaging Modalities Advisory Committee [MIIMAC] expert opinion).

MRA
Because of the closed space of an MRI, patients may experience feelings of claustrophobia, as well as being bothered by the noise; however, this may be less of a problem with new MRI machines, if available. It has been reported that up to 30% of patients experience apprehension and 5% to 10% endure some severe psychological distress, panic, or claustrophobia.[27,28] Some patients may have difficulty remaining still during the scan. Patients are not exposed to radiation during an MRI scan, which may be more acceptable to some.

U/S: Research from the literature demonstrates that, overall, patients are satisfied with U/S.[43,48]

Return to Summary Table.

CRITERION 7: Relative diagnostic accuracy of the test (link to definition)

One systematic review[12] was identified that evaluated the diagnostic accuracy of renal scintigraphy, U/S, CTA, and MRA using renal catheter angiography (RCA) as the gold standard. Receiver operating characteristic (ROC) curves were created for each test. Diagnostic accuracy

was measured as the area under the curve for each test. This MA was published in 2001 and included studies published up to August 2000. Because the MA was somewhat dated, a search for primary studies evaluating renal scintigraphy and at a least one of its alternatives (U/S, CTA, MRA, catheter angiography) published after 2000 was conducted. Seven primary studies were included: six comparing renal scintigraphy to catheter angiography,[19-24] two comparing renal scintigraphy to CTA,[21,25] two comparing renal scintigraphy to MRA,[21,25] and three comparing renal scintigraphy to U/S.[20,21,25] Table 3 provides an overview of the included studies reporting diagnostic accuracy data and the comparators included in each study (indicated by an X). Details of the diagnostic accuracy studies can be found in Appendix 3.

Table 3: Summary of Included Studies Reporting Diagnostic Accuracy

Date	Author	Study Type	RS vs. U/S	RS vs. CTA	RS vs. MRA	RS vs. RCA
2001	Vasbinder et al.[12]	SR/MA	X	X	X	X
2010	Abdulsamea et al.[24]	Obs				X
2010	Eriksson et al.[25]	Obs	X	X	X	
2006	Eklof et al.[21]	Obs	X	X	X	X
2003	Coen et al.[20]	Obs	X			
2002	Huot et al.[22]	Obs				X
2002	Karanikas et al.[23]	Obs				X
2001	Balink et al.[19]	Obs				X

CTA = computed tomography angiography; MA = meta-analysis; MRA = magnetic resonance angiography; Obs = observational study design; RCA = renal catheter angiography; RS = renal scintigraphy/scan; SR = systematic review; U/S = ultrasound; vs. = versus.

Renal scintigraphy versus catheter angiography

Table 4 presents the accuracy summary statistic reported in one systematic review[12] and the sensitivity and specificity reported in five primary studies[19,21-24] that compared renal scintigraphy with catheter angiography for the detection of renal hypertension. Sensitivity and specificity values for renal scintigraphy were estimated in the ranges of 48%[24] to 83%[19] (sensitivity) and 50%[21] to 75%[19] (specificity). Catheter angiography was the gold standard in the majority of studies comparing renal scintigraphy and catheter angiography.[12,19,22-24] Eklof et al. were the only authors to report sensitivity (95%) and specificity (91%) values for catheter angiography, using measurement of transstenotic pressure gradient as the gold standard.[21]

Table 4: Results from Studies Reporting Sensitivity, Specificity, or Accuracy of Renal Scintigraphy and Catheter Angiography

Author	Year	Renal Scintigraphy				Catheter Angiography			
		n	Acc (%)	Sens (%)	Spec (%)	n	Acc (%)	Sens (%)	Spec (%)
Meta-analysis									
Vasbinder et al.[12]	2001	14	92	NR	NR	Gold standard			
Primary studies									
Eklof et al.[21]	2006	56	NR	59	50	56	NR	95	91
Huot et al.[22]	2002	169	NR	74	59	Gold standard			

Balink et al.[19]	2001	158	NR	83	75	Gold standard
Karanikas et al.[23]	2002	33	NR	76	NR	Gold standard
Primary studies — pediatric population						
Abdulsamea et al.[24]	2009	49	NR	48	73	Gold standard

Acc = Accuracy; Sens = Sensitivity; Spec = Specificity; n = number of patients (or for meta-analysis = number of studies); NR =not reported.

Table 5 presents the positive and negative predictive values reported in primary studies comparing renal scintigraphy with catheter angiography. Coen et al. (2003),[20] Huot et al. (2002),[22] and Abdulsamea et al. (2010)[24] reported the positive predictive value of renal scintigraphy to be 0.72 , 0.58, and 0.76, respectively. Coen et al.,[20] Huot et al.,[22] and Abdulsamea et al.[24] reported the negative predictive value of renal scintigraphy to be 0.29, 0.75, and 0.51, respectively.

Table 5: Results from Studies Reporting Positive Predictive Value or Negative Predictive Value for Renal Scintigraphy and U/S

Author	Year	Renal Scintigraphy			Catheter Angiography		
		n	PPV	NPV	n	PPV	NPV
Primary studies							
Coen[20]	2003	35	0.72	0.29	Reference gold standard		
Huot[22]	2002	169	0.58	0.75	Reference gold standard		
Primary studies — pediatric population							
Abdulsamea[24]	2009	49	0.76	0.51	Reference gold standard		

n = number of patients or studies; NPV = negative predictive value; PPV = positive predictive value; U/S = ultrasound.

Renal scintigraphy versus CTA

Table 6 presents the accuracy summary statistic reported in one systematic review,[12] and the sensitivity and specificity reported in two primary studies[21,25] that compared renal scintigraphy with CTA for the detection of renal artery stenosis.

In their meta-analysis, Vasbinder et al. (2001)[12] calculated ROC curves for all the tests they evaluated including renal scintigraphy and CTA. The area under each test was used as a measurement of overall diagnostic accuracy. The overall accuracy of renal scintigraphy was estimated to be 92%, while the overall accuracy of CTA was estimated to be 99%. CTA was found to have a statistically significant better diagnostic accuracy than renal scintigraphy.

Eklof et al. (2006)[21] estimated the sensitivity and specificity to detect renal artery stenosis of a number diagnostic tests including renal scintigraphy and CTA in their prospective study of patients suspected of having RAS. Using the patient as the unit of analysis, the sensitivities of renal scintigraphy and CTA were estimated to be 59% and 100%, respectively. The specificities of renal scintigraphy and CTA were estimated to be 50% and 56%, respectively. The authors reported that the sensitivity of CTA was statistically significantly higher than that of renal scintigraphy.

Eriksson et al. (2010)[25] compared the diagnostic accuracy of renal scintigraphy and CTA in their prospective study of patients with mild renal impairment suspected of renal hypertension. The sensitivity and specificity of renal scintigraphy was reported to be 42% and 100%, respectively, with CTA as the gold standard.

Table 6: Results from Studies Reporting Sensitivity, Specificity, or Accuracy of Renal Scintigraphy and CTA									
Author	**Year**	**Renal Scintigraphy**				**CTA**			
		n	**Acc (%)**	**Sens (%)**	**Spec (%)**	**n**	**Acc (%)**	**Sens (%)**	**Spec (%)**
Meta-analysis									
Vasbinder[12]	2001	14	92	NR	NR.	5	99	NR	NR
Primary studies									
Eklof[21]	2006	56	NR	59	50	44	NR	100	56
Eriksson[25]	2010	47	NR	42	100	47	NR	Gold standard	

Acc = Accuracy; CTA = computed tomography angiography; n = number of patients (or for meta-analysis = number of studies); NR = not reported; Sens = Sensitivity; Spec = Specificity.

Renal scintigraphy versus MRA

Table 7 presents the accuracy summary statistic reported in one systematic review,[12] and the sensitivity and specificity reported in two primary studies[21,25] that compared renal scintigraphy with MRA for the detection of RAS. In their meta-analysis, Vasbinder et al. (2001)[12] calculated ROC curves for all tests they evaluated including renal scintigraphy and MRA. The area under each test was used as a measurement of overall diagnostic accuracy. The authors presented results separately for studies evaluating MRA with contrast and MRA without contrast. The overall accuracy of renal scintigraphy was estimated to be 0.92, while the overall accuracy of MRA with contrast was estimated to be 0.99. The overall accuracy of MRA without contrast was reported to be 0.97.

The authors found overall accuracy to be statistically significantly greater for both enhanced MRA and non-enhanced MRA compared with renal scinitigraphy. Eklof et al. (2006)[21] estimated the sensitivity and specificity to detect RAS of a number diagnostic tests including renal scintigraphy and MRA in their prospective study of patients suspected of having RAS. Using the patient as the unit of analysis, the sensitivity of renal scintigraphy and MRA was estimated to be 0.59 and 0.98, respectively. The specificity of renal scintigraphy and MRA was found to be 0.50 and 0.70, respectively. The authors report that sensitivity was statistically significantly greater for MRA compared with renal scintigraphy.

Eriksson et al. (2010)[25] compared the diagnostic accuracy of renal scintigraphy and U/S in their prospective study of patients with mild renal impairment suspected of renal hypertension. The sensitivity of renal scintigraphy and MRA was reported to be 0.42 and 0.81, respectively. The specificity of renal scintigraphy and U/S was found to be 1.0 and 0.79, respectively.

Table 7: Results from Studies Reporting Sensitivity, Specificity, or Accuracy of Renal Scintigraphy and MRA									
Author	**Year**	**Renal Scintigraphy**				**MRA**			
		n	**Acc**	**Sens**	**Spec**	**n**	**Acc**	**Sens**	**Spec**
Meta-analysis									
Vasbinder et al.[12]	2001	14	0.92	NR	NR	16	0.99	NR	NR
Primary studies									
Eklof et al.[21]	2006	56	NR	0.59	0.50	53	NR	0.98	0.70
Eriksson et al.[25]	2010	47	NR	0.42	1.00	45	NR	0.81	0.79

Acc = accuracy; n = number of patients (or for meta-analysis = number of studies); MRA = magnetic resonance angiography; NR = not reported; Sens = Sensitivity; Spec = Specificity.

Renal scintigraphy versus U/S

Table 8 presents the accuracy summary statistic reported in one systematic review,[12] and the sensitivity and specificity reported in two primary studies[21,25] that compared renal scintigraphy with U/S for the detection of renal hypertension. In their meta-analysis, Vasbinder et al. (2001)[12] calculated ROC curves for all the tests they evaluated including renal scintigraphy and U/S. The area under each test was used as a measurement of overall diagnostic accuracy. The overall accuracy of renal scintigraphy was estimated to be 0.92, while the overall accuracy of U/S was estimated to be 0.93. No statistical difference was found between the overall accuracy of renal scintigraphy and U/S.

Eklof et al. (2006)[21] estimated the sensitivity and specificity to detect RAS of a number of diagnostic tests including renal scintigraphy and U/S in their prospective study of patients suspected of having RAS. Using the patient as the unit of analysis, the sensitivity of renal scintigraphy and U/S was estimated to be 0.59 and 0.80, respectively. The specificity of renal scintigraphy and U/S was found to be 0.50 and 0.54, respectively. The authors report that sensitivity was statistically significantly better for U/S compared to renal scintigraphy.

Eriksson et al. (2010)[25] compared the diagnostic accuracy of renal scintigraphy and U/S in their prospective study of patients with mild renal impairment suspected of renal hypertension. The sensitivity of renal scintigraphy and U/S was reported to be 0.42 and 0.70, respectively. The specificity of renal scintigraphy and U/S was found to be 1.0 and 0.89, respectively.

Table 8: Results from Studies Reporting Sensitivity, Specificity, or Accuracy of Renal Scintigraphy and U/S

Author	Year	Renal Scintigraphy				Ultrasonography			
		n	Acc	Sens	Spec	n	Acc	Sens	Spec
Meta-analysis									
Vasbinder et al.[12]	2001	14	0.92	NR	NR	24	0.93	NR	NR
Primary studies									
Eklof et al.[21]	2006	56	NR	0.59	0.50	57	NR	0.80	0.54
Eriksson et al.[25]	2010	47	NR	0.42	1.00	36	NR	0.70	0.89

Acc = Accuracy; n = number of patients (or for meta-analysis = number of studies); NR = not reported; Sens = Sensitivity; Spec = Specificity.

Table 9 presents the positive and negative predictive values reported in primary studies comparing renal scintigraphy with U/S. Coen et al. (2003)[20] reported the positive predictive value of renal scintigraphy and U/S to be 0.722 (95% CI, 0.465 to 0.903) and 0.943 (95% CI, 0.808 to 0.993) respectively. The negative predictive value of renal scintigraphy and U/S was reported to be 0.294 (95% CI, 0.103 to 0.56) and 0.870 (95% CI, 0.664 to 0.972), respectively.

Table 9: Results from Studies Reporting Positive and Negative Predictive Values or Renal Scintigraphy and U/S

Author	Year	Renal Scintigraphy			Ultrasonography		
		n	PPV	NPV	n	PPV	NPV

Coen et al.[20]	2003	35	0.722	0.294	35	0.943	0.870

n = number of patients; NPV = negative predictive value; PPV = positive predictive value; U/S = ultrasound.

Other

It should be noted that not all people with RAS have renovascular hypertension, and not all patients with renovascular hypertension and RAS will necessarily benefit from surgical intervention (MIIMAC expert opinion). The objective of the study by Krijnen and colleagues was to identify subgroups of patients with hypertension and RAS who benefit from immediate intervention with costly angioplasty and drug therapy.[49] Of 106 patients with RAS (≥ 50% of lumen diameter by digital subtraction angiography), the authors found that only those patients with bilateral RAS benefited from immediate intervention with angioplasty. Patients had a normal or mildly impaired renal function (serum creatinine concentration ≤ 2.3 mg/dL) at study entry but, after one year of follow-up, their renal function had improved if angioplasty had taken place immediately after diagnosis. However, renal function deteriorated if angioplasty had been delayed for three months. None of the other subgroups had a clear benefit of immediate intervention regarding renal function or blood pressure control.

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CRITERION 8: Relative risks associated with the test (link to definition)

Non–radiation-related Risks

Renal scintigraphy: Adverse events from renal scintigraphy are rare but may include allergy to the radiopharmaceutical, rash, fever, or chills.[31] There is also a relative contraindication in the administration of captopril in patients with a solitary kidney, as it may precipitate transient acute renal failure if the kidney has physiologically significant RAS (MIIMAC expert opinion).

Catheter angiography: Risks of catheter angiography include side effects from contrast dye that is used during the procedure, arterial occlusion, and damage to the artery or artery wall, which can lead to blood clots.[7]

CTA: Patients may experience side effects from contrast dye that is sometimes injected into the patient before imaging. A recent large retrospective study found that 0.15% of patients given CT contrast material experienced side effects.[32] Most of these were mild side effects such as nausea, vomiting and hives. The percentage of patients experiencing a serious side effect (defined as cardiovascular collapse, moderate or severe bronchospasm, laryngeal edema, loss of consciousness, or seizure) was 0.005%.[32]

MRA: MRA (which uses an MRI machine) does not expose patients to any radiation.[33] Patients undergoing MRA may experience headaches, sweating, nausea, and fatigue. Patients may experience side effects from contrast dye that is sometimes injected into the patient before imaging. A recent large retrospective study found that 0.04% of patients given MRA contrast material experienced side effects.[32] Most of these were mild side effects such as nausea, vomiting, and hives. Serious side effects (defined as cardiovascular collapse, moderate or severe bronchospasm, laryngeal edema, loss of consciousness, or seizure) occurred in 0.003% of patients. Toxicity of the MRA contrast agent Gd is of particular concern for patients with renal failure. In such patients, Gd has been linked to nephrogenic fibrosis, a serious disease affecting the skin, internal organs, and muscles.[34]

U/S: U/S does not expose patients to any radiation.[33] There are no reported risks associated with U/S in the literature that was reviewed.

Radiation-related Risks

Among the diagnostic tests for renal hypertension, renal scintigraphy, RCA, and CTA expose the patient to ionizing radiation. The average effective radiation dose delivered with these procedures is reported in Table 10. The biological effects of this low-dose radiation remain unclear. In 2003, Brenner et al. reviewed the epidemiological evidence regarding low-dose radiation exposure and concluded that there is good evidence of an increase in risk of cancer at acute doses greater than 50 millisievert (mSv), and reasonable evidence for an increase in some cancer risks at doses above about 5 mSv.[50]

Table 10: Effective Radiation Doses for Various Imaging Tests

Test	Effective Radiation Dose (mSv)
^{99m}Tc-DTPA renal scan	1.8[35]
^{99m}Tc-MAG3 renal scan	2.6[35]
Catheter angiography	2.36[51]
CTA	8.0[35]
MRA	0
U/S	0
Average background dose of radiation per year	1 to 3.0[35-37]

CTA = computed tomography angiography; MRA = magnetic resonance angiography; mSv = millisievert; ^{99m}Tc-DTPA = technetium-99m-labelled- diethylenetriamine pentaacetic acid; ^{99m}Tc-MAG3 = technetium-99m-labelled mercaptoacetyl triglycine; U/S = ultrasound.

Renal scintigraphy: The radioisotopes used in scintigraphy expose patients to radiation. As shown in Table 10, the average effective dose for renal scintigraphy using ^{99m}Tc-DTPA is 1.8 mSv. The average effective dose for renal scintigraphy using ^{99m}Tc-MAG3 is 2.6 mSv.[35] This can be compared with the average annual effective dose from background radiation of about 1 to 3 mSv.[35-37]

Catheter angiography: Renal catheter angiography exposes patients to radiation. As shown in Table 10, the average effective dose for RCA is 2.36 mSv.[51]

CTA: As shown in Table 10, the average effective radiation dose for abdominal CT is 8.0 mSv.[35]

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CRITERION 9: Relative availability of personnel with expertise and experience required for the test (link to definition)

The personnel required for the performance of the imaging tests to evaluate renovascular hypertension are presented by modality. A summary of the availability of personnel required for the conduct of renal scanning or any of the alternative imaging modalities is provided in Table 11. No information was found regarding the number of radiologists specialized in interventional radiology.

Renal scintigraphy: In Canada, physicians involved in the performance, supervision, and interpretation of renal scans should be nuclear medicine physicians or diagnostic radiologists with training/expertise in nuclear imaging. Nuclear medicine technologists are required to conduct renal scintigraphy. Technologists must be certified by the Canadian Association of Medical Radiation Technologists (CAMRT) or an equivalent licensing body.

All alternative imaging modalities: Service engineers are needed for system installation, calibration, and preventive maintenance of the imaging equipment at regularly scheduled intervals. The service engineer's qualification will be ensured by the corporation responsible for service and the manufacturer of the equipment used at the site. Qualified medical physicists (on site or contracted part-time) should be available for the installation, testing, and ongoing quality control of CT, MRI, U/S machines, and nuclear medicine equipment.[52]

Catheter angiography: To perform RCA, diagnostic radiologists must have a thorough understanding of vascular anatomy, angiographic equipment, and radiation safety considerations.[7] Medical radiation technologists (MRTs) must be certified by CAMRT or an equivalent licensing body.

CTA: For the performance of CT scan, MRTs who are certified by CAMRT or an equivalent licensing body recognized by CAMRT are required.

MRA: Medical technologists must have CAMRT certification in magnetic resonance or be certified by an equivalent licensing body recognized by CAMRT.

U/S: Sonographers (or ultrasonographers) should be graduates of an accredited school of sonography or have obtained certification by the Canadian Association of Registered Diagnostic Ultrasound Professionals (CARDUP). They should be members of their national or provincial professional organization. Sonography specialties include general sonography, vascular sonography, and cardiac sonography.[38] In Quebec, sonographers and MRTs are grouped together; in the rest of Canada, sonographers are considered a distinct professional group.[38]

Table 11: Medical Imaging and Relevant Health Professionals in Canada[38]

Jurisdiction	Diagnostic Radiology Physicians	Nuclear Medicine Physicians	MRTs	Nuclear Medicine Technologists	Sonographers	Medical Physicists
NL	46	3	263	15	NR	NR
NS	71	5	403	71	NR	NR
NB	47	3	387	55	NR	NR
PEI	7	0	57	3	NR	0
QC	522	90	3,342	460	NR	NR
ON	754	69	4,336	693	NR	NR
MB	58	8	501	42	NR	NR
SK	61	4	359	36	NR	NR
AB	227	18	1,229	193	NR	NR
BC	241	21	1,352	212	NR	NR
YT	0	0	–	–	NR	0
NT	0	0	26	1	NR	0
NU	0	0	–	–	NR	0

Table 11: Medical Imaging and Relevant Health Professionals in Canada[38]						
Jurisdiction	**Diagnostic Radiology Physicians**	**Nuclear Medicine Physicians**	**MRTs**	**Nuclear Medicine Technologists**	**Sonographers**	**Medical Physicists**
Total	**2,034**	**221**	**12,255**	**1,781**	**2,900***	**322***

AB = Alberta; BC = British Columbia; MB = Manitoba; NB = New Brunswick; MRT = medical radiation technologist; NL = Newfoundland and Labrador; NR = not reported by jurisdiction; NS = Nova Scotia; NT= Northwest Territories; NU = Nunavut; ON = Ontario; PEI= Prince Edward Island; QC = Quebec; YT = Yukon.
* This represents a total for all of the jurisdictions.

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CRITERION 10: Accessibility of alternative tests (equipment and wait times) (link to definition)

There are notable variations in the availability of medical imaging technologies within hospitals across Canada. Nuclear medicine cameras are not available in the Yukon, the Northwest Territories, and Nunavut. Table 12 provides an overview of the availability of equipment required to evaluate renovascular hypertension. Data for nuclear medicine cameras (including SPECT) are current to January 1, 2007. The number of CT, MRI, and SPECT/CT scanners is current to January 1, 2010. Data were not available for U/S.

Renal scintigraphy
For renal scans, nuclear medicine facilities with gamma cameras (including SPECT) are required. Three jurisdictions — the Yukon, the Northwest Territories, and Nunavut — do not have any nuclear medicine equipment.[40] In 2007, the latest year for which data are available, the average time for renal scintigraphy in McGill University Health Centre (MUHC) hospitals was 13 days. However, the wait times were reported to be less than one day for emergency cases.[39]

Catheter Angiography
Renal catheter angiography requires the use of an angiography suite. As of 2007, there were 179 angiography suites available in Canada. This is equivalent to 5.5 angiography suites per one million people.[38] Based on the experiences of hospitals in a large Canadian city, the average wait time for an elective angiography procedure was 21 days.[39] The average wait time for an emergency angiography was 12 hours.[39]

CTA
No CT scanners are available in Nunavut.[38] The average weekly use of CT scanners ranged from 40 hours in Prince Edward Island to 69 hours in Ontario, with a national average of 60 hours.[38] In 2010, the average wait time for a CT scan in Canada is 4.2 weeks.[41]

MRA
No MRI scanners are available in the Yukon, Northwest Territories, or Nunavut.[38] According to CIHI's National Survey of Selected Medical Imaging Equipment database, the average number of hours of operation per week for MRI scanners in 2006–2007 ranged from 40 hours in Prince Edward Island to 99 hours in Ontario, with a national average of 71 hours.[38] In 2010, the average wait time for MR imaging in Canada was 9.8 weeks.[41]

U/S
U/S machines are widely available across the country. According to the Fraser Institute, the average wait time for U/S in 2010 was 4.5 weeks.[41]

Table 12: Diagnostic Imaging Equipment in Canada[38,40]					
	Nuclear Medicine Cameras	**Angiography Suites**	**CT Scanners**	**MRI Scanners**	**SPECT/CT Scanners**
Number of devices	603[38]	179[38]	460[40]	218[40]	96[40]
Average number of hours of operation per week (2006-2007)[38]	40	39	60	71	n/a
Provinces and Territories with no devices available	YT, NT, NU	YT, NT, NU	NU	YT, NT, NU	PEI, YT, NT, NU

CT = computed tomography; MRI = magnetic resonance imaging; NT = Northwest Territories; NU = Nunavut; PEI = Prince Edward Island; SPECT = single-photon emission computed tomography; YT= Yukon.

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CRITERION 11: Relative cost of the test (link to definition)

Fee codes from the Ontario Schedule of Benefits were used to estimate the relative costs of Captopril-enhanced renal scintigraphy and its alternatives. Technical fees are intended to cover costs incurred by the hospital (i.e., radiopharmaceutical costs, medical/surgical supplies, and non-physician salaries). Maintenance fees are not billed to OHIP — estimates here were provided by St. Michael's Hospital in Toronto. Certain procedures (i.e., PET scan, CT scan, MRI scan) are paid for, in part, out of the hospital's global budget; these estimates were provided by The Ottawa Hospital. It is understood that the relative costs of imaging will vary from one institution to the next.

According to our estimates (Table 13), the cost of scintigraphy with ^{99m}Tc-based radioisotopes is $327.38. There is essentially no difference between the cost of renal scintigraphy and the cost of CT. Magnetic resonance angiography and RCA are moderately more costly tests. U/S is a minimally less costly alternative.

Table 13: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[53]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
Renal scintigraphy				
J835	Computer-assessed renal function — includes first transit	135.10	73.00	208.10
J880	Computer-assessed renal function — repeat after pharmacological intervention	46.00	22.50	68.50
Maintenance fees — from global budget		50.78		50.78
	TOTAL	231.88	95.50	**327.38**
CT				
X126	CT — abdomen — with and without IV contrast		114.00	114.00
Technical cost — from global budget		150.00		150.00

Table 13: Cost Estimates Based on the Ontario Schedule of Benefits for Physician Services Under the *Health Insurance Act* (September 2011)[53]				
Fee Code	**Description**	**Tech. Fees ($)**	**Prof. Fees ($)**	**Total Costs ($)**
Maintenance fees — from global budget		42.82		42.82
	TOTAL	192.82	114.00	**306.82**
MRA				
X451C	MRA — abdomen — multislice sequence		77.20	77.20
X455C (×3)	Repeat (another plane, different pulse sequence; to a maximum of 3 repeats)		38.65 (×3) = 115.95	115.95
X487C	When gadolinium is used		38.60	38.60
X499C	3-D MRI acquisition sequence, including post-processing (minimum of 60 slices; maximum 1 per patient per day)		65.40	65.40
Technical cost — from global budget		300.00		300.00
Maintenance fees — from global budget		73.00		73.00
	TOTAL	373.00	297.15	**670.15**
Renal catheter angiography				
X181B and X181C	Abdominal, thoracic, cervical, or cranial angiogram by catheterization — using film changer, cine, or multiformat camera — non-selective	61.20	32.50	93.70
X182B and X182C (×2)	Abdominal, thoracic, cervical, or cranial angiogram by catheterization — using film changer, cine, or multiformat camera — selective (per vessel, 2)	81.35 (×2) = 162.70	39.40 (×2) = 78.80	241.50
J021	Angiography — by catheterization — abdominal, thoracic, cervical, or cranial — insertion of catheter (including cut-down, if necessary), and injection, if given		121.40 (spec) 90.06 (anes)	211.46
J022 (x2)	selective catheterization — add to catheter insertion fee (per vessel, 2)		60.15 (x2) = 120.30	120.30
Maintenance fees — from global budget		51.00		51.00
	TOTAL	274.9	443.06	**717.96**
U/S				
J135	Abdominal scan — complete	50.00	34.95	84.95
Maintenance fees — from global budget		3.30		3.30
	TOTAL	53.30	34.95	**88.25**

3-D = three-dimensional; CT = computed tomography; IV = intravenous; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; Prof. = professional; Tech. = technical.; U/S = ultrasound.

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APPENDIX

Appendix 1: Multi-Criteria Decision Analysis Definitions

Domain 1: Criteria Related to the Underlying Health Condition	
Criterion	**Definition**
1. Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and which may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.
2. Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.
3. Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing the test, in whatever way, on the expected mortality of the underlying condition. Measures could include survival curves showing survival over time, and/or survival at specific time intervals with and without the test.
4. Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the test, in whatever way, on the expected morbidity or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures such as events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales with and without the test.
Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
5. Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socioeconomic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test that are in population groups with disproportionate burdens. (Explanatory note: The implication of this definition is that, everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens.)
6. Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, as well as other burdens. This

Domain 2: Criteria Comparing ^{99m}Tc with an Alternative, or Comparing between Clinical Uses	
Criterion	**Definition**
	criterion does not include risks of adverse events but is about everything related to the experience of undergoing the test.
7. Relative diagnostic accuracy of the test	Ability of the test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.
8. Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.
9. Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.
10. Accessibility of alternatives (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives. Excludes any limitation on accessibility related to human resources considerations.
11. Relative cost of the test	Operating cost of test (e.g., consumables, heath care professional reimbursement) compared with alternatives.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Ovid MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE <1948 to April 5, 2011>
Date of Search:	April 6, 2011
Alerts:	Weekly search updates began April 6, 2011 and ran until October 2011.
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, and diagnostic accuracy studies.
Limits:	No date limit for systematic reviews; publication years 2001 – April 2011 for primary studies English language Human limit for primary studies

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical subject heading
.fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
?	Truncation symbol for one or no characters only
ADJ	Requires words are adjacent to each other (in any order)
ADJ#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word: usually includes subject headings and controlled vocabulary
.tw	Text word: searches title, abstract, captions, and full text
.mp	Keyword search: includes title, abstract, name of substance word, subject heading word and other text fields
.pt	Publication type
.nm	Name of substance word: used to search portions of chemical names and includes words from the CAS Registry/EC Number/Name (RN) fields
.jw	Journal words: searches words from journal names
/du	Diagnostic use
/ri	Radionuclide imaging

Ovid MEDLINE Strategy	
Line #	**Search Strategy**
1	Technetium/
2	exp Technetium Compounds/
3	exp Organotechnetium Compounds/
4	exp Radiopharmaceuticals/
5	radioisotope*.mp.
6	(technetium* or Tc-99* or Tc99* or Tc-99m* or Tc99m* or 99mTc* or 99m-Tc* or 99mtechnetium* or 99m-technetium*).tw,nm.

Ovid MEDLINE Strategy	
7	Radionuclide Imaging/ or Perfusion Imaging/ or Radioisotope Renography/
8	ri.fs.
9	((radionucl* or nuclear or radiotracer* or perfusion or gamma camera*) adj2 (imag* or scan* or test* or diagnos*)).tw.
10	(SPECT or scintigraph* or scintigram* or scintiphotograph* or scintiscan*).tw.
11	Tomography, Emission-Computed, Single-Photon/
12	(single-photon adj2 emission*).tw.
13	((renal* or kidney*) adj7 (imaging or perfusion* or scan*)).tw.
14	(renograp* or reno-graph* or renogram*).tw.
15	(MAG3 or MAG-3 or Mercaptoacetyltriglycine or Mertiatide or TechneScan or Mercaptoacetylglycylglycylglycine or Mercaptoacetyl triglycine).tw.
16	(DTPA or diethylenetriaminepentaacetic acid* or diethylenetriamine penta-acetic acid*).tw.
17	125224-05-7.rn.
18	or/1-17
19	exp Hypertension, Renal/
20	((renal or reno-vascular* or renovascular*) adj3 hypertensi*).tw.
21	(goldblatt adj (syndrome or hypertensi*)).tw.
22	Renal Artery Obstruction/
23	(renal adj3 (obstruction* or stenos* or stenotic lesion*)).tw.
24	or/19-23
25	Meta-Analysis.pt.
26	Meta-Analysis/ or Systematic Review/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/
27	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).tw.
28	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).tw.
29	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).tw.
30	(data synthes* or data extraction* or data abstraction*).tw.
31	(handsearch* or hand search*).tw.
32	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).tw.
33	(met analy* or metanaly* or health technology assessment* or HTA or HTAs).tw.
34	(meta regression* or metaregression* or mega regression*).tw.

Ovid MEDLINE Strategy	
35	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
36	(medline or Cochrane or pubmed or medlars).tw,hw.
37	(cochrane or health technology assessment or evidence report).jw.
38	or/25-37
39	exp "Sensitivity and Specificity"/
40	False Positive Reactions/
41	False Negative Reactions/
42	du.fs.
43	sensitivit*.tw.
44	(predictive adj4 value*).tw.
45	distinguish*.tw.
46	differentiat*.tw.
47	enhancement.tw.
48	identif*.tw.
49	detect*.tw.
50	diagnos*.tw.
51	accura*.tw.
52	comparison*.tw.
53	Comparative Study.pt.
54	(Validation Studies or Evaluation Studies).pt.
55	Randomized Controlled Trial.pt.
56	Controlled Clinical Trial.pt.
57	(Clinical Trial or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
58	Multicenter Study.pt.
59	(random* or sham or placebo*).ti.
60	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti.
61	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti.
62	(control* adj3 (study or studies or trial*)).ti.
63	(non-random* or nonrandom* or quasi-random* or quasirandom*).ti.
64	(allocated adj "to").ti.
65	Cohort Studies/
66	Longitudinal Studies/
67	Prospective Studies/
68	Follow-Up Studies/
69	Retrospective Studies/

Ovid MEDLINE Strategy	
70	Case-Control Studies/
71	Cross-Sectional Study/
72	(observational adj3 (study or studies or design or analysis or analyses)).ti.
73	cohort.ti.
74	(prospective adj7 (study or studies or design or analysis or analyses or cohort)).ti.
75	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti.
76	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data or cohort)).ti.
77	(retrospective adj7 (study or studies or design or analysis or analyses or cohort or data or review)).ti.
78	((case adj control) or (case adj comparison) or (case adj controlled)).ti.
79	(case-referent adj3 (study or studies or design or analysis or analyses)).ti.
80	(population adj3 (study or studies or analysis or analyses)).ti.
81	(cross adj sectional adj7 (study or studies or design or research or analysis or analyses or survey or findings)).ti.
82	or/39-81
83	Case Reports.pt.
84	82 not 83
85	18 and 24 and 38
86	limit 85 to english language
87	18 and 24 and 84
88	limit 87 to (english language and humans and yr="2001 -Current")

OTHER DATABASES	
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Cochrane Library Issue 1, 2011	Same MeSH, keywords, and date limits used as per MEDLINE search, excluding study types and Human restrictions. Syntax adjusted for Cochrane Library databases.

Grey Literature

GREY LITERATURE SEARCHING	
Dates for Search:	April 2011
Keywords:	Included terms for radionuclide imaging and renal hypertension.
Limits:	No limits

The following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for evidence-based medicine” (CADTH Grey Matters checklist) were searched:

- Health Technology Assessment Agencies (selected)
- Clinical Practice Guidelines
- Databases (free)
- Internet Search.

Appendix 3: Study Descriptions

Vasbinder et al.[12]

Vasbinder et al.[12] conducted a systematic review and meta-analysis of studies evaluating the diagnostic accuracy of non-invasive or minimally invasive tests for the diagnosis of renal hypertension. The tests that were considered included captopril renal scintigraphy, computed tomography angiography (CTA), magnetic resonance angiography (MRA), and ultrasound (U/S). The authors searched MEDLINE, Embase and Cochrane databases for relevant articles. In order to be included in the meta-analysis, studies had to have the following characteristics:

- use renal catheter angiography (RCA) as the gold standard test
- have a patient population suspected of renal hypertension
- the criteria for a positive test result was explicitly stated
- the number of patients by diagnosis status (i.e., true-positives, false-negatives, true-negatives, false-positives) reported or able to be derived from data presented.

Diagnostic data from included studies were pooled by creating receiver-operator characteristic (ROC) curves for each test. The diagnostic performance of each test was measured by the area under the ROC for each test. A higher area under the curve indicated better diagnostic performance.

The number of studies identified in the literature search that evaluated captopril scintigraphy, U/S, CTA, and MRA was 172, 314, 343, and 306, respectively. The number of studies that were included in the meta-analysis for captopril scintigraphy, U/S, CTA, and MRA was 14, 24, five, and 16, respectively. The area under the ROC curve for captopril renal scintigraphy was calculated to be 0.92. Compared with renal scintigraphy, the area under the ROC curve was estimated to be higher for ultrasonography (0.93), CTA (0.99), and MRA (0.99 gadolinium-enhanced, 0.97, non–gadolinium-enhanced). Based on between-test comparisons, captopril renal scintigraphy had a statistically significantly worse diagnostic performance compared with CTA, gadolinium-enhanced MRA and non–gadolinium-enhanced MRA. No statistically significant difference was found between captopril renal scintigraphy and U/S.

The authors concluded that their main finding was that MRA and CTA has better diagnostic accuracy than the other test evaluated, including renal scintigraphy. However, they do offer some potential methodological issues. Specifically, they state that the use of catheter renal angiography as the gold standard may lead to underestimation of the diagnostic accuracy of functional tests such as renal scintigraphy. They also note that the unit of analysis for MRA and CTA was most often at the artery level, while for renal scintigraphy people were most often used as the unit of analysis. They speculate that this may overestimate the diagnostic accuracy of MRA and CTA compared with renal scintigraphy.

Abdulsamea et al.[24]

Abdulsamea et al. evaluated the diagnostic accuracy of captopril renal scintigraphy in children suspected of having renal artery stenosis. Subjects included all children (age ≤18 years) that were investigated with both renal scintigraphy and digital subtraction angiography between 1986 and 2008 in a hospital in Egypt. All subjects had hypertension and were suspected of having renal artery stenosis.

Pre- and post-captopril tests were performed separately with both technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) and technetium-99m mercaptoacetyl triglycine (^{99m}Tc-MAG3). Based on 81 patients, the sensitivity and specificity of a combination of

^{99m}Tc-DMSA and ^{99m}Tc-MAG3 renal scintigraphy studies were 0.48 and 0.73, respectively. The positive predictive value and negative predictive value of renal scintigraphy were reported to be 0.76 and 0.51, respectively. The authors also reported diagnostic accuracy separately for renal scintigraphy using ^{99m}Tc-DMSA and ^{99m}Tc-MAG3. The sensitivity and specificity of scintigraphy using the ^{99m}Tc-DMSA was reported to be 0.46 and 0.90, respectively. The sensitivity and specificity of scintigraphy using the ^{99m}Tc-MAG3 was reported to be 0.45 and 0.85, respectively.

Ericksson et al.[25]

Ericksson et al.[25] investigated the accuracy of various diagnostic tests in patients with moderate renal impairment suspected of having renal artery stenosis. The study was comprised of 47 consecutive adult patients from a Swedish hospital, with moderate renal impairment (serum creatine 150-300 µmol/L) and with suspicion of renal hypertension. Patients were investigated with captopril renal scintigraphy plus renin analysis, magnetic resonance angiography (MRA), and computed tomography angiography (CTA) within a two-day period. Though not part of the original protocol, 36 of the 47 patients also underwent Doppler U/S. The authors reported the sensitivity and specificity of various diagnsotic tests using CTA as the reference standard. A positive test result was defined as CTA with ≥ 50% diameter reduction.

The sensitivity of MRA (n = 45), U/S (n = 36), and renal scintigraphy (n = 47) was reported to be 0.806 (95% Confidence Interval [CI], 0.625 to 0.925), 0.704 (95% CI, 0.498 to 0.862), and 0.424 (95% CI, 0.255 to 0.608), respectively. The specificity of MRA (n = 45), U/S (n = 36), and renal scintigraphy (n = 47) was reported to be 0.786 (95% CI, 0.492 to 0.953), 0.889 (95% CI, 0.518 to 0.997), and 1.0 (95% CI, 0.807 to 1.0), respectively.

The authors also presented the sensitivity and specificity of alternatives evaluated on the kidney level instead of the patient level. The sensitivity of MRA, U/S, and renal scintigraphy evaluated at the kidney level was reported to be 0.756, 0.528, and 0.295, respectively. The specificity of MRA, U/S, and renal scintigraphy evaluated at the kidney level was reported to be 0.816, 0.806, and 0.860, respectively.

The authors also reported diagnostic accuracy using “functional and morphologic stenosis” as an alternate gold standard. Based on this gold standard, RAS was defined as positive if either CTA and MRA showed ≥ 50% diameter reduction and either renal scintigraphy plus rennin or U/S indicated the presence of significant stenosis.

Based on this alternate gold standard, the sensitivity of CTA (n = 34), MRA (n = 434), U/S (n = 34), and renal scintigraphy (n = 34) was reported to be 1.00 (95% CI, 0.867 to 1.000), 0.90 (95% CI, 0.683 to 0.988), 0.905 (95% CI, 0.696 to 0.988), and 0.667 (95% CI, 0.430 to 0.854), respectively. If it is assumed that the threshold for a positive test is 70% diameter reduction, the sensitivity for CTA and MRA decreases to 0.810 and 0.600, respectively.

The specificity of CTA (n = 34), MRA (n = 34), U/S (n = 34), and renal scintigraphy (n = 34) was reported to be 0.615 (95% CI, 0.316 to 0.681), 0.692 (95% CI, 0.386 to 0.909), 1.0 (95% CI, 0.794 to1.000), and 1.0 (95% CI, 0.794 to 1.000), respectively. If the threshold for a positive test was assumed to be 70% diameter reduction, the specificity for CTA and MRA becomes 1.0 and 0.846, respectively.

The authors also presented the sensitivity and specificity of alternatives evaluated on the kidney level instead of the patient level. Using the alternate reference standard, the sensitivity of CTA, MRA, U/S, and renal scintigraphy evaluated at the kidney level was reported to be 0.964, 0.852,

0.714, and 0.5005, respectively. The specificity of MRA, U/S, and renal scintigraphy evaluated at the kidney level was reported to be 0.758, 0.788, 0.970, and 0.970, respectively.

Eklof et al.[21]

In a prospective study, Eklof et al.[21] evaluated the diagnostic accuracy of four non-invasive tests to detect renal artery stenosis. The tests evaluated included captopril renal scintigraphy, U/S, CTA, and MRA. Renal catheter angiography with pressure gradient measurement was used as the gold standard test. Specifically, the gold standard was digital subtraction angiography (DSA) with transstenotic pressure gradient measurement (PGM).

Patients with suspicion of RAS were recruited from various departments of a Swedish hospital. A total of 58 patients participated in the study. The number of patients who underwent captopril renal scintigraphy, U/S, CTA, and MRA were 56, 57, 44, and 53, respectively. The median time from first exam to RCA was two days. ^{99m}Tc-MAG3 was used as the radiopharmaceutical for captopril renal scintigraphy. The authors state that renal scintigraphy findings were classified as low, intermediate, or high probability of renal artery stenosis. The authors state that the scoring classification is based on guidelines, which are referenced. Details of the guidelines were not provided in the article. Tests that were scored high or intermediate probability of RAS were considered to be positive.

The authors state that the criteria for a positive U/S test was based on aortic and renal artery peak systolic velocity (PSV). For MRA, CTA, and RCA, the degree of stenosis was assessed by comparing the diameter of the narrowest stenotic segment with the diameter of a normal renal artery segment.

Sensitivity and specificity were estimated on both a per person basis and on a per kidney basis. On a per patient basis, the sensitivity of renal scintigraphy, U/S, CTA, MRA, and digital subtraction angiography was estimated to be 0.59, 0.80, 1.0, 0.98, and 0.95, respectively. Specificity was estimated to be 0.50, 0.54, 0.56, 0.70, and 0.91, respectively.

Based on a per kidney basis, the sensitivity of renal scintigraphy, U/S, CTA, MRA, and digital subtraction angiography was estimated to be 0.52, 0.73, 0.94, 0.93, and 0.91, respectively. Specificity was estimated to be 0.63, 0.71, 0.62, 0.91, and 0.93, respectively. The authors found that sensitivity was statistically significantly higher in U/S, CTA, and MRA compared with renal scintigraphy.

Coen et al.[20]

Coen et al.[20] investigated the diagnostic performance of duplex U/S and renal scintigraphy to in-patients with either arterial hypertension or chronic renal disease suspected of renal artery stenosis. The study investigated 269 consecutive patients referred to an Italian nephrology clinic with arterial hypertension, chronic renal failure, or both. Renal angiography by means of MRA or RCA was considered the gold standard.

For U/S, the criteria for significant stenosis were:

- systolic peak velocity above 180 cm/sec
- and renal aortic ratio defined as the ratio between systolic peak velocity in the renal artery and peak velocity in the abdominal aorta in the supra-renal tract with a normal value of < 3.5.

Renal scintigraphy was performed with a gamma camera, with either ^{99m}Tc-DTPA or ^{99m}Tc-MAG3. Criteria for a positive test were:

- parenchymal transit time > 4 minutes
- a difference in split renal function > 30%
- T_{max} > 5 minutes, with a difference between kidneys >1 minute.

A captopril test was performed in 161 out of the 224 patients undergoing renal scintigraphy. Criteria for a positive test following captopril administration with ^{99m}Tc-DTPA is a fall in glomerular filtration rate of the affected side > 5%. With ^{99m}Tc-MAG3, the criteria were an increase of at least 0.15 of the 20 minutes/peak count ratio; or a lengthening of > 2minutes of T_{max}, or a delay of tracer elimination in the pelvis of > 2 minutes.

Of the 49 patients that had a Doppler U/S positive for renal artery stenosis, 35 received either MRA or RCA. Based on these 35 patients, the positive predictive value for U/S was reported to be 94.3% (80.8%, 99.3%). The negative predictive value was found to be 87.0% (66.4%, 97.2%).

Of the 24 patients that had a Doppler U/S positive for renal artery stenosis, 18 received either MRA or RCA. Of the 200 negative cases, 17 patients underwent angiography. Based on the 35 patients that received both renal scintigraphy and angiography, the positive predictive value for scintigraphy was reported to be 0.722 (0.465, 0.903). The negative predictive value was found to be 0.294 (0.103, 0.56).

Huot et al.[22]

Huot et al.[22] conducted a retrospective study to investigate the diagnostic accuracy of captopril renal scintigraphy. Subjects included all patients at an American hospital who underwent both renal scintigraphy and RCA within a six-month period. Kidneys were the unit of analysis. A total of 169 kidneys from 86 patients were included in the analysis. Results from the RCA were considered the gold standard.

The criteria for a positive renal scintigraphy included:

- time to peak activity of more than 11 minutes on either pre-captopril or post-captopril scan
- or glomerular filtration greater than 1.5 between the two kidneys on the post-captopril scan.

Criteria of positive test results for RCA were stenosis of more than 75% or stenosis of more than 50%, with post-stenotic dilatation.

The sensitivity and specificity of renal scintigraphy was found to be 0.74 (0.62, 0.86) and 0.59 (0.49, 0.69), respectively. The positive predictive value of renal scintigraphy was reported to be 0.58 (0.47, 0.68), while the negative predictive value was estimated to be 0.75 (0.64, 0.84).

Karanikas et al.[23]

Karanikas et al.[23] compared the sensitivity of captopril renal scintigraphy with valsartan renal scintigraphy. Valsartan is an angiotensin receptor blocker. The study included 25 hypertensive patients confirmed to have renal artery stenosis by means of RCA. The 25 patients in the study had a total of 33 stenosed vessels. Vessels were the unit of analysis.

All subjects received captopril scintigraphy, valsartan scintigraphy, and baseline renal scintigraphy within 48 hours. ^{99m}Tc-MAG3 was used as the radiopharmaceutical for all renal scintigraphy tests.

Criteria for a positive captopril renal scintigraphy and valsartan renal scintigraphy were either:

- an increase in T_{max} of at least two minutes or 40% after captopril or valsartan compared with baseline scintigraphy
- or an increase of at least 0.15 in the ratio of the amplitude at 20 minutes to the amplitude at T_{max} of the curves after captopril or valsartan scintigraphy.

A criterion for a positive test with RCA was 50% or greater stenosis.

The authors reported the sensitivity for captopril renal scintigraphy to be 0.76. This compares to a sensitivity of 0.30 found for valsartan renal scintigraphy.

Balink et al.[19]

Balink et al.[19] studied the diagnostic accuracy of captopril renal scintigraphy using bilateral identical curves. The study population included 158 patients suspected of renal hypertension undergoing both renal scintigraphy and RCA.

Criteria for a positive renal scintigraphy was relative uptake in one of the kidneys of < 40% or if the T_{max} in one or both kidneys was ≥ to six minutes. A criterion for a positive RCA was renal artery stenosis of 50% or more.

The authors reported the sensitivity of renal scintigraphy to be 0.83, while the specificity of renal scintigraphy was estimated to be 0.75. In the 42 patients that had bilateral renal artery stenosis detected by RCA, renal scintigraphy diagnosed 0.46 of patients as having bilateral renal artery stenosis.

Krijnen et al.[49]

In a secondary analysis of the DRASTIC (Dutch Renal Artery Stenosis Intervention Cooperative) study, Krijnen and colleagues retrospectively evaluated different subgroups of patients: patients with positive captopril-renin scintigraphy, abnormal captopril renogram, recently developed hypertension, bilateral stenosis, and severe stenosis.[49] The authors found that only those patients with bilateral RAS benefited from immediate intervention with balloon angioplasty. Patients had a normal or mildly impaired renal function (serum creatinine concentration ≤ 2.3 mg/dL) at study entry; but after one year of follow-up, their renal function had improved if angioplasty had taken place immediately after diagnosis, although renal function deteriorated if angioplasty had been delayed for three months. None of the other subgroups had a clear benefit of immediate intervention regarding renal function or blood pressure control.

Appendix 3: Rating Tool

Table A1: Domain 1 — Criteria Related to the Underlying Health Condition								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
#1: Size of the affected population	The estimated size of the patient population that is affected by the underlying health condition and that may potentially undergo the test. The ideal measure is point prevalence, or information on how rare or common the health condition is.	N/A	N/A	N/A	≤ 1 in 10,000 (0.01%)	> 1 in 10,000 (0.01%) and ≤ 1 in 1,000 (0.1%)	> 1 in 1,000 (0.1%) and ≤ 1 in 100 (1%)	> 1 in 100 (1%)
#2: Timeliness and urgency of test results in planning patient management	The timeliness and urgency of obtaining the test results in terms of their impact on the management of the condition and the effective use of health care resources.	N/A	N/A	N/A	Situations that would score 0 include: a) when the target time frame for performing the ^{99m}Tc-based test is > 30 days, or obtaining the test results in the appropriate	Situations that would score 1 include: a) when the target time frame for performing the ^{99m}Tc-based test is between 8 and 30 days and obtaining the test results in the appropriate	Situations that would score 2 include: a) when the target time frame for performing the ^{99m}Tc-based test is between 8 and 30 days and obtaining the test results in the appropriate timely	Situations that would score 3 include: a) when the target time frame for performing the test is in 24 hours or less and obtaining the test results in the appropriate timely

Table A1: Domain 1 — Criteria Related to the Underlying Health Condition								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
					timely manner for the underlying condition has no impact on the management of the condition or the effective use of health care resources b) target time frame for performing the ^{99m}Tc-based test is between 8 and 30 days and obtaining the test results in the appropriate timely manner for the underlying condition has minimal	timely manner for the underlying condition has moderate impact on the management of the condition or the effective use of health care resources b) target time frame for performing the test is between 2 and 7 days and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has minimal impact on the management of the condition or the effective	manner for the underlying condition has significant impact on the management of the condition or the effective use of health care resources b) target time frame for performing the test is between 2 and 7 days and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has moderate impact on the management of the condition or the effective use of health care resources c) target time	manner for the underlying condition has moderate to significant impact on the management of the condition or the effective use of health care resources b) when the target time frame for performing the test is in 2 to 7 days and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has significant impact on

Table A1: Domain 1 — Criteria Related to the Underlying Health Condition								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
					impact on the management of the condition or the effective use of health care resources	use of health care resources	frame for performing the test is in 24 hours or less and obtaining the ^{99m}Tc-based test results in the appropriate timely manner for the underlying condition has minimal impact on the management of the condition or the effective use of health care resources	the management of the condition or the effective use of health care resources
#3: Impact of not performing a diagnostic imaging test on mortality related to the underlying condition	Impact of not performing a diagnostic imaging test, in whatever way, on the expected mortality from the underlying condition. Measures could include survival curves showing survival over time and/or	N/A	N/A	N/A	Diagnostic imaging test results have no impact on mortality	Diagnostic imaging test results can have minimal impact on mortality	Diagnostic imaging test results can have moderate impact on mortality	Diagnostic imaging test results can have significant impact on mortality

Table A1: Domain 1 — Criteria Related to the Underlying Health Condition								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
	survival at specific time intervals with and without the test.							
#4: Impact of not performing a diagnostic imaging test on morbidity or quality of life related to the underlying condition	Impact of not performing the diagnostic imaging test, in whatever way, on the expected morbidity, or on the quality of life reduction of the underlying condition. Measures of impact may include natural morbidity outcome measures, like events or disease severity, or might be expressed using generic or disease-specific quality of life rating scales, with and without the test.	N/A	N/A	N/A	Diagnostic imaging test results have no impact on morbidity or quality of life	Diagnostic imaging test results can have minimal impact on morbidity or quality of life	Diagnostic imaging test results can have moderate impact on morbidity or quality of life	Diagnostic imaging test results can have significant impact on morbidity or quality of life

Table A2: Domain 2 — Criteria Comparing a ^{99m}Tc-based Test with an Alternative								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
#5: Relative impact on health disparities	Health disparities are defined as situations where there is a disproportionate burden (e.g., incidence, prevalence, morbidity, or mortality) amongst particular population groups (e.g., gender, age, ethnicity, geography, disability, sexual orientation, socio-economic status, and special health care needs). Impact on health disparities is assessed by estimating the proportion of current clients of the ^{99m}Tc-based test who are in population groups with disproportionate burdens. Note: The implication of this	The size of the patient population belonging to one of more disadvantaged groups is > 10% lower than the average for all clinical uses of ^{99m}Tc	The size of the patient population belonging to one of more disadvantaged groups is 6% to 10% lower than the average for all clinical uses of ^{99m}Tc	The size of the patient population belonging to one of more disadvantaged groups is 1% to 5% lower than the average for all clinical uses of ^{99m}Tc	The size of the patient population belonging to one of more disadvantaged groups is equal to average for all clinical uses of ^{99m}Tc	The size of the patient population belonging to one of more disadvantaged groups is 1% to 5% higher than the average for all clinical uses of ^{99m}Tc	The size of the patient population belonging to one of more disadvantaged groups is 6% to 10% higher than the average for all clinical uses of ^{99m}Tc	The size of the patient population belonging to one of more disadvantaged groups is > 10% higher than the average for all clinical uses of ^{99m}Tc

Table A2: Domain 2 — Criteria Comparing a ^{99m}Tc-based Test with an Alternative								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
	definition is that everything else being the same, it is preferable to prioritize those clinical uses that have the greatest proportion of clients in groups with disproportionate burdens).							
#6: Relative acceptability of the test to patients	Acceptability of the ^{99m}Tc-based test from the patient's perspective compared with alternatives. Patient acceptability considerations include discomfort associated with the administration of the test, out-of-pocket expenses or travel costs, factors that may cause great inconvenience to patients, and other burdens. This criterion does not include	^{99m}Tc-based test is significantly less acceptable to patients	^{99m}Tc-based test is moderately less acceptable to patients	^{99m}Tc-based test is minimally less acceptable to patients	^{99m}Tc-based test and alternative test are similarly acceptable to patients	^{99m}Tc-based test is minimally more acceptable to patients	^{99m}Tc-based test is moderately more acceptable to patients	^{99m}Tc-based test is significantly more acceptable to patients

Table A2: Domain 2 — Criteria Comparing a ^{99m}Tc-based Test with an Alternative								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
	risks of adverse events, but is about everything related to the experience of undergoing the test.							
#7: Relative diagnostic accuracy of the test	Ability of the ^{99m}Tc-based test to correctly diagnose the patients who have the condition (sensitivity) and patients who do not have the condition (specificity) compared with alternatives.	Diagnostic accuracy of the ^{99m}Tc-based test is significantly lower than alternative	Diagnostic accuracy of the ^{99m}Tc-based test is moderately lower than alternative	Diagnostic accuracy of the ^{99m}Tc-based test is minimally lower	^{99m}Tc-based test and alternative test have similar diagnostic accuracies	Diagnostic accuracy of the ^{99m}Tc-based test is minimally better than alternative	Diagnostic accuracy of the ^{99m}Tc-based test is moderately better than alternative	Diagnostic accuracy of the ^{99m}Tc-based test is significantly better than alternative
#8: Relative risks associated with the test	Risks associated with the test (e.g., radiation exposure, side effects, adverse events) compared with alternatives. Risks could	^{99m}Tc-based test is significantly less safe	^{99m}Tc-based test is moderately less safe	^{99m}Tc-based test is minimally less safe	^{99m}Tc-based test and alternative have similar safety profiles	^{99m}Tc-based test is minimally more safe	^{99m}Tc-based test is moderately more safe	^{99m}Tc-based test is significantly more safe

Table A2: Domain 2 — Criteria Comparing a ^{99m}Tc-based Test with an Alternative								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
	include immediate safety concerns from a specific test or long-term cumulative safety concerns from repeat testing or exposure.							
#9: Relative availability of personnel with expertise and experience required for the test	Availability of personnel with the appropriate expertise and experience required to proficiently conduct the test and/or interpret the test findings compared with alternatives.	N/A	N/A	N/A	> 95% of the procedures can be performed in a timely manner using the alternative, assuming the necessary equipment is available.	75% to 94% of the procedures can be performed in a timely manner using the alternative, assuming the necessary equipment is available.	25% to 74% of the procedures can be performed in a timely manner using the alternative, assuming the necessary equipment is available.	< 25% of the procedures can be performed in a timely manner using the alternative, assuming the necessary equipment is available.
#10: Accessibility of alternative tests (equipment and wait times)	Availability (supply) of equipment and wait times for alternative tests within the geographic area. Includes consideration of the capacity of the system to accommodate increased demand for the alternatives.	N/A	N/A	N/A	> 95% of the procedures can be performed in a timely manner using alternative, assuming that the necessary expertise is available.	75% to 94% of the procedures can be performed in a timely manner using alternative, assuming that the necessary expertise is available.	25% to 74% of the procedures can be performed in a timely manner using alternative, assuming that the necessary expertise is available.	< 25% of the procedures can be performed in a timely manner using alternative, assuming that the necessary expertise is available.

Table A2: Domain 2 — Criteria Comparing a ^{99m}Tc-based Test with an Alternative								
Criterion	**Definition**	**–3**	**–2**	**–1**	**0**	**1**	**2**	**3**
	Excludes any limitation on accessibility related to human resources considerations							
#11: Relative cost of the test	Operating cost of test (e.g., consumables, health care professional reimbursement fees) compared with alternatives.	Cost of the ^{99m}Tc-based test is significantly higher than alternative (i.e., incremental cost increase exceeds $501)	Cost of the ^{99m}Tc-based test is moderately higher than alternative (i.e., incremental cost increase is between $251 and $500)	Cost of the ^{99m}Tc-based test is minimally higher than alternative (i.e., incremental cost increase is between $26 and $250)	No difference in the cost of ^{99m}Tc-based test and alternative (i.e., incremental cost is between $0 and $25)	Cost of the ^{99m}Tc-based test is minimally lower than alternative (i.e., incremental cost decrease is between $26 and $250)	Cost of the ^{99m}Tc-based test is moderately lower than alternative (i.e., incremental cost decrease is between $251 and $500)	Cost of the ^{99m}Tc-based test is significantly lower than alternative (i.e., incremental cost decrease exceeds $501)

^{99m}Tc = technetium-99m.

Appendix 4: Weighted Composite Scores

Table A3: Final Ranking of Clinical Uses and Alternatives to ^{99m}Tc-based Imaging

Clinical Use	Weighted Composite Score	Alternative
Detection of lower GI bleeding	**200**	**AA**
Assessment of bile leak	**139**	**U/S**
	152	MRCP
	165	CT
	177	ERCP
Detection of pulmonary embolism	**135**	**CTPA**
Diagnosis of (osteoporotic) fracture	**132**	**MRI**
	134	CT
	183	^{18}F-PET
Diagnosis of acute osteomyelitis (children)	**131**	**CT**
	137	U/S
	157	MRI
Imaging for metastatic disease (breast)	**125**	**^{18}F-PET**
	142	^{18}FDG-PET
Imaging for metastatic disease (lung)	**118**	**^{18}FDG-PET**
	125	^{18}F-PET
Assessment of prognosis post-myocardial infarction	**117**	**Echo**
	120	^{201}Tl-SPECT MPI
	130	PET
	135	MRI
	137	CTCA
Detection of ischemia	**117**	**Echo**
	120	^{201}Tl-SPECT MPI
	130	PET
	135	MRI
	137	CTCA
Imaging for metastatic disease (prostate)	**113**	**^{18}F-PET**
Preoperative assessment prior to vascular, non-cardiac surgery	**108**	**Echo**
	111	^{201}Tl-SPECT MPI
	121	PET
	126	MRI
	128	CTCA
Evaluation of painful prosthesis (loosening)	**101**	**Arthrography**
	145	^{18}F-PET
ICD decision-making	**99**	**Echo**
	124	MRI
Diagnosis of acute cholecystitis	**96**	**U/S**
	121	MRCP
	134	CT
Evaluation of renal function — post-transplant	**90**	**U/S**
Evaluation of painful prosthesis (infection)	**85**	**^{111}In-WBC**
	101	Arthrography
	169	^{18}FDG-PET
Assessment of drug-induced cardiotoxicity	**82**	**Echo**
	107	MRI
Diagnosis of acute osteomyelitis (adults)	**72**	**MRI**
	77	^{111}In-WBC

Table A3: Final Ranking of Clinical Uses and Alternatives to ^{99m}Tc-based Imaging		
Clinical Use	**Weighted Composite Score**	**Alternative**
	93	CT
	130	^{18}FDG-PET
Diagnosis of avascular necrosis	**70**	**MRI**
SLNB	**67**	**Blue Dye**
	119	ALND
Suspected obstructive uropathy (adults)	**64**	**U/S**
	107	MRU
Suspected obstructive uropathy (children)	**64**	**U/S**
	132	MRU
Evaluation of renal function — renovascular hypertension	**62**	**U/S**
	83	CT
	97	MRA
	115	RCA
Diagnosis of (stress) fracture	**57**	**MRI**
	59	CT
	108	^{18}F-PET

AA = abdominal angiography; ALND = axillary lymph node dissection; CT = computed tomography; CTCA = computed tomography coronary angiography; Echo = echocardiography; ^{18}F-PET = ^{18}F-labelled sodium fluoride positron emission tomography; ^{18}FDG-PET = ^{18}F-labelled fluorodeoxyglucose positron emission tomography; ^{111}In-WBC = indium-111–labelled white blood cell scan; MRA = magnetic resonance angiography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; MRU = magnetic resonance urography; PET = positron emission tomography; RCA = renal catheter angiography; ^{99m}Tc = technetium-99m; ^{201}Tl-SPECT MPI = thallium-201–labelled single-photon emission tomography myocardial perfusion imaging; U/S = ultrasound.

Note: numbers in bold represent the best alternative to ^{99m}Tc-based imaging based on the criteria assessed.

Appendix 5: Criteria Ratings for All Clinical Uses

Table A4: Individual Ratings for Each Clinical Use of ^{99m}Tc

Clinical Use	Size of Affected Population	Timeliness and Urgency	Impact on Mortality	Impact on Morbidity	Alternative to ^{99m}Tc-Based Imaging Test	Health Disparities*	Acceptability to Patients	Diagnostic Accuracy	Risk	Personnel	Equipment	Cost
Detection of lower GI bleeding	1	3	1	2	AA	0	3	3	3	2	2	3
Assessment of bile leak	1	3	2	3	CT	0	1	2	1	0	0	1
					ERCP	0	3	–2	3	3	2	3
					MRCP	0	–1	0	–1	2	2	2
					U/S	0	–1	2	–1	0	0	–1
Detection of pulmonary embolism	2	3	3	2	CTPA	0	–1	0	1	0	0	–1
Diagnosis of (osteoporotic) fracture	2	3	2	3	CT	0	0	0	0	0	0	–1
					MRI	0	–1	–1	–1	1	1	1
					^{18}F-PET	0	–1	0	0	3	3	3
Diagnosis of acute osteomyelitis (children)	2	3	0	3	CT	0	1	2	0	0	0	–1
					MRI	0	2	1	1	1	2	1
					U/S	0	–1	3	–1	2	0	–2
Imaging for metastatic disease (breast)	2	2	0	3	^{18}FDG-PET	0	0	0	0	3	3	3
					^{18}F-PET	0	–1	–1	0	3	3	3
Imaging for metastatic disease (lung)	2	2	0	3	^{18}FDG-PET	0	0	–2	0	3	3	3
					^{18}F-PET	0	–1	–1	0	3	3	3
Assessment of prognosis post-myocardial infarction	2	2	2	2	CTCA	0	–1	1	0	2	2	–2
					Echo	0	–1	0	0	2	1	–2
					MRI	0	0	–1	0	3	3	–1
					PET	0	–1	–1	0	2	3	1
					^{201}TI-SPECT	0	0	1	0	0	0	0
Detection of ischemia	2	2	2	2	CTCA	0	–1	1	0	2	2	–2
					Echo	0	–1	0	0	2	1	–2

Table A4: Individual Ratings for Each Clinical Use of ^{99m}Tc													
Clinical Use	**Size of Affected Population**	**Timeliness and Urgency**	**Impact on Mortality**	**Impact on Morbidity**	**Alternative to ^{99m}Tc-Based Imaging Test**	**Health Disparities***	**Acceptability to Patients**	**Diagnostic Accuracy**	**Risk**	**Personnel**	**Equipment**	**Cost**
					MRI	0	0	–1	0	3	3	–1
					PET	0	–1	–1	0	2	3	1
					^{201}Tl-SPECT	0	0	1	0	0	0	0
Imaging for metastatic disease (prostate)	2	2	0	3	^{18}FDG-PET	0	–1	–2	0	3	3	3
Preoperative assessment prior to vascular, non-cardiac surgery	1	2	2	2	CTCA	0	–1	1	0	2	2	–2
					Echo	0	–1	0	0	2	1	–2
					MRI	0	0	–1	0	3	3	–1
					PET	0	–1	–1	0	2	3	1
					^{201}Tl-SPECT	0	0	1	0	0	0	0
Evaluation of painful prosthesis (loosening)	1	1	1	3	Arthrography	0	2	0	2	0	0	–1
					^{18}FDG-PET	0	1	0	1	3	3	3
ICD decision-making	1	2	3	1	Echo	0	–1	1	–1	0	0	–1
					MRI	0	–1	0	–1	2	2	2
Diagnosis of acute cholecystitis	1	3	1	2	CT	0	1	2	1	0	0	1
					MRCP	0	–1	0	–1	2	2	2
					U/S	0	–1	1	–1	0	0	1
Evaluation of renal function — post-transplant	0	3	1	3	U/S	0	–1	0	–1	0	0	–1
Evaluation of painful prosthesis (infection)	1	1	1	3	Arthrography	0	2	0	2	0	0	–1
					^{18}FDG-PET	0	1	2	1	3	3	3
					^{111}In-WBC	0	0	–2	1	1	1	2
Assessment of drug-induced cardiotoxicity	1	2	1	2	Echo	0	–1	1	–1	0	0	1
					MRI	0	–1	0	–1	2	2	2
Diagnosis of acute osteomyelitis	1	2	0	2	CT	0	1	2	0	0	0	–1

Table A4: Individual Ratings for Each Clinical Use of ^{99m}Tc												
Clinical Use	**Size of Affected Population**	**Timeliness and Urgency**	**Impact on Mortality**	**Impact on Morbidity**	**Alternative to ^{99m}Tc-Based Imaging Test**	**Health Disparities***	**Acceptability to Patients**	**Diagnostic Accuracy**	**Risk**	**Personnel**	**Equipment**	**Cost**
(adults)					^{18}FDG-PET	0	–1	1	1	3	3	3
					^{111}In-WBC	0	0	–1	1	1	1	1
					MRI	0	–1	0	–1	1	2	1
Diagnosis of avascular necrosis	1	2	0	2	MRI	0	–1	–1	–1	1	2	1
SLNB	1	3	0	3	ALND	0	3	0	1	0	0	1
	1	3	0	0	Blue dye alone	0	–1	1	0	2	0	–1
Suspected obstructive uropathy (adults)	1	1	0	2	MRU	0	–1	2	–1	3	2	2
					U/S	0	–1	2	–1	0	0	–1
Suspected obstructive uropathy (children)	1	1	0	2	MRU	0	2	2	1	3	2	2
					U/S	0	–1	2	–1	0	0	–1
Evaluation of renal function — renovascular hypertension	2	1	1	1	CTA	0	2	0	2	0	0	0
					MRA	0	–1	0	1	2	2	2
					RCA	0	3	–1	3	2	2	2
					U/S	0	–1	0	–1	2	0	–1
Diagnosis of (stress) fracture	2	1	0	2	CT	0	0	0	0	0	0	–1
					MRI	0	–1	–1	–1	1	1	1
					^{18}F-PET	0	–1	0	0	3	3	3

AA = abdominal angiography; ALND = axillary lymph node dissection; CT = computed tomography; CTCA = computed tomography coronary angiography; CTPA = computed tomography pulmonary angiography; Echo = echocardiography; ERCP = endoscopic retrograde cholangiopancreatography; ^{18}F-PET = ^{18}F-labelled sodium fluoride positron emission tomography; ^{18}FDG-PET = ^{18}F-labelled fluorodeoxyglucose positron emission tomography; GI = gastrointestinal; ICD = implantable cardioverter-defibrillator; ^{111}In-WBC = indium-111–labelled white blood cell scan; MRA = magnetic resonance angiography; MRCP = magnetic resonance cholangiopancreatography; MRI = magnetic resonance imaging; MRU = magnetic resonance urography; PET = positron emission tomography; RCA = renal catheter angiography; SLNB = sentinel lymph node biopsy; ^{99m}Tc = technetium-99m; ^{201}Tl-SPECT MPI = thallium-201–labelled single-photon emission tomography myocardial perfusion imaging; U/S = ultrasound.

*The relative impact of the health disparities criterion was not rated at the national level by MIIMAC; therefore, a rating of 0 was arbitrarily selected for scoring purposes.