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PET Diagnostic Imaging with Prostate-Specific Membrane Antigen for Prostate Cancer: A Review of Clinical Utility, Cost-Effectiveness, Diagnostic Accuracy, and Guidelines

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Abbreviations

AGREE	Appraisal of Guidelines for Research and Evaluation
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
ASTRO	American Society for Radiation Oncology
AUA	American Urological Association
BCR	biochemical recurrence
COI	conflict of interest
CT	computed tomography
DOR	diagnostic odds ratio
DR	disease detection rate
LR-	negative likelihood ratio
LR+	positive likelihood ratio
MA	meta-analysis
MRI	magnetic resonance imaging
NPV	negative predictive value
PET	positron emission tomography
PPV	positive predictive value
PSA	prostate specific antigen
PSMA	prostate specific membrane antigen
SR	systematic review
SUO	Society of Urologic Oncology
US	United States

Context and Policy Issues

Prostate cancer diagnosis affects over 1.1 million men worldwide annually and one in eight Canadian males will experience the disease in their lifetimes.[1,2] Following primary treatment options with curative intent, including surgical or radiation therapy, patients with prostate cancer experience a recurrence rate of between 27% and 53% at 10 years.[1,3] Recurrence is most often detected by surveillance of prostate-specific antigen (PSA), with biochemical recurrence (BCR) defined as reaching threshold serum PSA levels following primary treatment.[3,4] Treatment options for patients with BCR of prostate cancer are determined by the source(s) of increased PSA levels, either locally confined recurrence or metastatic disease.[5] Imaging of patients with recurrence of prostate cancer is used to determine the disease localization and severity. The diagnostic performance of imaging in these patients is therefore of critical importance to personalized treatment planning.[6,7]

The sensitivity of conventional imaging modalities, such computed tomography (CT), magnetic resonance imaging (MRI), and bone scan, often fails to detect sites of relapse and/or metastasis.[3,8] Positron emission tomography imaging has improved upon these conventional imaging modalities using radiolabeled tracers including ^{11}C-Choline, ^{18}F-FCholine, and ^{18}F-Fluciclovine.[3] These radiolabeled tracers enable detection of common cancer cell characteristics. Prostate-specific membrane antigen (PSMA) is a well-validated alternative target with specificity for prostate cancer.[9] Radioligands targeting PSMA, such as ^{68}Ga-PSMA-11, have demonstrated increased diagnostic sensitivity using PET imaging.[3,9-12]

This report aims to retrieve and review the cost-effectiveness, diagnostic accuracy, and evidence-based guidelines regarding PSMA PET imaging for patients with suspected or confirmed metastatic or BCR of prostate cancer.

Research Questions

1. What is the cost-effectiveness of PET imaging using PSMA labelled with gallium-68 (^{68}Ga) or fluorine-18 (^{18}F) in patients with suspected or confirmed metastatic or biochemically recurrent prostate cancer?
2. What is the diagnostic accuracy of PET imaging using PSMA labelled with ^{68}Ga or ^{18}F in patients with suspected or confirmed metastatic or biochemically recurrent prostate cancer?
3. What are the evidence-based guidelines regarding the use of PET imaging using prostate-specific membrane antigen (PSMA) labelled with ^{68}Ga or fluorine-18 ^{18}F in patients with suspected or confirmed metastatic or biochemically recurrent prostate cancer?

Key Findings

Prostate-specific membrane antigen (PSMA) positron emission tomography (PET) imaging for patients with biochemical recurrence of prostate cancer was evaluated as a cost-effective alternative to usual care imaging in one well-conducted economic analysis. The applicability of this study to the Canadian healthcare setting was not clear and the study was limited by the sources of clinical and cost data inputs. Evidence identified on the diagnostic accuracy of PSMA PET imaging consisted of 197 relevant primary studies compiled in 16 systematic reviews included in this report. This large body of evidence was evaluated by 11 of the included systematic reviews as having significant risk of bias, most commonly associated with the diagnostic reference standard. Additionally, four systematic reviews found evidence of possible publication bias in favour of positive results within the primary study evidence. Despite high heterogeneity and a lack of consistent diagnostic performance outcomes between primary studies, a consensus that PSMA PET provided useful diagnostic performance for recurrent prostate cancer was reported by the systematic reviews. Evidence was also identified from four systematic reviews that suggested that PSMA PET provided greater diagnostic accuracy than radiolabeled choline-based PET. There was also consensus that PSMA PET diagnostic accuracy decreased with decreasing prostate-specific antigen (PSA) levels in biochemical recurrence, as observed with other PET radiolabeled tracers. One meta-analysis also reported statistically superior disease detection of PSMA PET as compared to radiolabeled choline PET imaging in patients with lower PSA levels. The authors of the majority of systematic reviews concluded that larger prospective comparative trials with a suitable and consistent reference standard are

required to accurately determine diagnostic accuracy of PSMA PET and thereby its optimal role in diagnosing patients with recurrence of prostate cancer. One set of guidelines from the US had a relevant recommendation, based on expert opinion, that PET/CT including PSMA PET imaging may be used for patients with biochemical recurrence of prostate cancer as an alternative to conventional imaging.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including MEDLINE, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. 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 prostate specific membrane antigen and prostatic neoplasms. Search filters were applied to limit retrieval to economic studies, health technology assessments, systematic reviews, meta-analyses, or network meta-analyses, and guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2019 and October 17, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (any age) previously diagnosed with prostate cancer with suspected or confirmed metastatic or biochemically recurrent prostate cancer.
Intervention	Positron emission tomography (PET) imaging using prostate-specific membrane antigen (PSMA) labelled with gallium-68 (Ga-68) or fluorine-18 (F-18)
Comparator	Q1: Prostate-specific antigen (PSA) blood testing, bone scan, CT, MRI, biopsy, PET or PET-CT imaging using other prostate cancer-specific PET radiotracers (e.g., ^{18}F-fluorodeoxyglucose [^{18}F-FDG], ^{18}F-sodium fluoride [^{18}F-NaF], ^{11}C-Choline, ^{18}F-FCholine, ^{18}F-fluciclovine), active surveillance, or watchful waiting Q2: Bone scan, CT, MRI, PET or PET-CT imaging using other prostate cancer-specific PET radiotracers (e.g., ^{18}F-fluorodeoxyglucose [^{18}F-FDG], ^{18}F-sodium fluoride [^{18}F-NaF], ^{11}C-Choline, ^{18}F-FCholine, ^{18}F-fluciclovine), or no comparator test Q3: Not applicable
Outcomes	Q1: Cost-effectiveness (e.g., quality-adjusted life year [QALY], incremental cost-effectiveness ratio [ICER], cost per patient adverse event avoided, cost per clinical outcome, cost minimization) Q2: Diagnostic accuracy (e.g., sensitivity, specificity, accuracy, positive predictive value [PPV], negative predictive value [NPV], disease detection rate) Q3: Recommendations regarding the use of PET imaging using PSMA labelled with ^{68}Ga or ^{18}F in patients with suspected or confirmed prostate cancer (e.g., optimal radiotracer)
Study Designs	Health technology assessments, systematic reviews, economic evaluations, and evidence-based guidelines.

CT = computed tomography; PET = positron emission tomography; PSMA = prostate-specific membrane antigen

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2019. The identification of several recently published systematic reviews, collectively covering 197 relevant primary studies, negated the need for inclusion of primary studies to address the research questions.

Critical Appraisal of Individual Studies

The included publications were critically appraised by one reviewer using the following tools as a guide: A MeaSurement Tool to Assess systematic Reviews 2 (AMSTAR 2)[13] for systematic reviews, the Drummond checklist[14] for economic evaluations, and the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument[15] for guidelines. Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included publication were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 104 citations were identified in the literature search. Following screening of titles and abstracts, 81 citations were excluded and 23 potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publication were retrieved from the grey literature search for full-text review. Of the 25 potentially relevant articles, seven publications were excluded for various reasons, and 18 publications met the inclusion criteria and were included in this report. These comprised 16 systematic reviews,[3-12,16-21] one economic evaluation,[1] and one evidence-based guideline published as two parts.[22,23] Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[24] flowchart of the study selection.

The overlap of primary study evidence reviewed by the included SRs is presented in Appendix 5. Evidence from primary studies included in multiple SRs may be overrepresented in the data presented and findings have not been adjusted for potential overrepresentation in this report.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided in Appendix 2.

Study Design

One economic evaluation was identified and included in this report.[1] The analysis was an exploratory cost-effectiveness analysis, modelling a ten-year time horizon from the perspective of the Australian health system. The model used was a decision-analytic tree with Markov chains and employed clinical data from a pilot study of 30 patients with BCR of prostate cancer following primary curative treatment of surgery or radiotherapy. Healthcare costs were obtained from the Australian Medicare costing schedules while costing of the tracer and imaging was from a hospital imaging department and expert opinion. Follow-up occurred every six months with PSMA PET/MRI or usual care. Modeled false positives incurred the costs of nodal and distant disease management with the survival probability of local disease, while modeled false negatives incurred costs of local disease management with the survival expectations of nodal or distant cancer.[1]

A total of 16 SRs fit the inclusion criteria presented in Table 1 and addressed diagnostic accuracy of PSMA PET imaging,[3-12,16-21] eight of which were published in 2019,[5,8,10,11,16,18,19,21] and eight of which were published in 2020.[3,4,6,7,9,12,17,20] One SR examined published meta-analyses and identified and included 39 published MAs.[4] The other 15 SRs included all study designs in the selection criteria, and all reported that the majority of the identified and included studies were retrospective observational studies.[3,5-12,16-21] Overall this body of evidence cited 197 studies used to summarize evidence relevant to this report which was a subset of the total number of studies cited by the SRs. A summary of the overlap of relevant studies contained in this body of evidence is presented in Appendix 5.

One set of evidence-based guidelines was identified that had relevant recommendations regarding PSMA PET imaging for patients with BCR of prostate cancer.[22,23] These guidelines were developed by the American Urological Association (AUA), the American Society for Radiation Oncology (ASTRO), and the Society of Urologic Oncology (SUO). The guidelines were developed using a systematic literature search, a risk of bias assessment, grading of the strength of evidence, and a consensus on the data synthesis for recommendation formulation. Both a strength of recommendation and a strength of the supporting evidence were reported for each recommendation. The strength of evidence was graded A (highest) to C (lowest), while recommendations were graded strong, moderate, or conditional based on the available evidence, or in cases for which there may or may not be evidence in the medical literature recommendations were graded as a clinical principle, or expert opinion.

Country of Origin

The economic analysis originated in Australia, and the clinical data was collected in an Australian health care setting. The study is presented in Australian dollars (AUD) however all outcomes are also reported in US$, OECD Purchasing Power Parities, and the authors argue that the clinical and economic outcomes of the study should apply to patients outside of Australia.[1]

First authors of the included SRs reported being based in institutions located in Switzerland,[4,18,19] US,[3,8,10,16,17] Italy,[6] Austria,[7] Japan,[7] France,[12] Australia,[9] China,[20,21] Belgium,[5] and the UK.[11]

The guidelines were written by a development group from the US however the location of the intended users of the recommendations was not defined.[22,23]

Patient Population

Gordon et al. obtained clinical data for the economic model from 30 patients with BCR of prostate cancer after primary curative treatment, either surgery (n = 23) or radiotherapy (n = 7). Patients with BCR of prostate cancer with PSA over 0.2ng/mL on at least two occasions following radical prostatectomy, or PSA equal to or greater than 2.0 ng/mL above nadir two years post radiotherapy were eligible. Patients were excluded if they were under 18 years of age, were administered a radioisotope within five half-lives prior to enrolment, were unable to physically comply or had a contraindication to PET scan or PSMA ligand, or had another malignancy within the prior two years.[1]

Of the included SRs, three examined broader research questions on patients with prostate cancer, whether it was advanced prostate cancer or not. These three SRs did contain analyses specific to patients with advanced prostate cancer.[4,6,9] The remaining 13 SRs

included studies that enrolled patients with advanced prostate cancer.[3,5,7,8,10-12,16-21] Advanced prostate cancer was defined as biochemical recurrence,[3,7,8,10,16-20] metastatic prostate cancer,[12] recurrent prostate cancer,[5,11] or prostate cancer that had metastasized to bone.[21]

The guidelines from AUA/ASTRO/SUO were for patients with advanced prostate cancer. Recommendations for prognosis and treatment were specific to patients with prostate cancer and BCR without metastatic disease after exhaustion of local treatment options, metastatic hormone-sensitive prostate cancer, non-metastatic castration-resistant prostate cancer, or metastatic castration-resistant prostate cancer.[22,23]

Interventions and Comparators

The economic evaluation, Gordon et al., examined the cost-efficacy of ^{68}Ga-PSMA-11 PET/MRI imaging to usual care imaging. The authors used a detection rate (DR) of 61% for ^{68}Ga-PSMA-11 PET/MRI and a DR of 22% for usual care imaging (CT and bone scan). Patients were followed-up every six months with either imaging interventions. Follow-up imaging costs were AU$1811 for the ^{68}Ga-PSMA-11 imaging strategy and AU$2291 for the usual care strategy. Clinical data inputs of mortality estimates were based upon cited literature and included a 2.5% annual increase when androgen deprivation therapy was delayed, and a 2.2% mortality for local disease with surveillance. Other mortality estimates were tabulated such as mortality following radiotherapy (70 GY and 79 GY) of both local and nodal stages, with and without androgen deprivation therapy. The authors reported a qualitatively high rate of histologic biopsy validation of the imaging findings.[1]

All included SRs reported evidence specific to PSMA PET imaging interventions, however the SRs varied in the intervention of interest. Turpin et al. and De Visschere et al. conducted a SR for any imaging modality.[5,12] Annunziata et al., examined any PET imaging.[4] Evangelista examined any PET/MRI imaging. The remaining SRs had some differences in their focus on a PSMA radioligand PET imaging intervention with PSMA PET/CT (i.e. any PSMA radioligand);[3,11,19,21] PSMA PET (i.e. PET/MRI or PET/CT with any PSMA radioligand);[7,16] ^{68}Ga-PSMA-11 PET (i.e PET/MRI or PET/CT);[9,10] ^{68}Ga or ^{18}F-PSMA PET/CT;[17] ^{68}Ga-PSMA-11 PET/MRI;[20] PET/CT using either ^{18}F-FACBC, or ^{68}Ga-PSMA;[8] or ^{18}F-PSMA PET/CT.[18] Ten SRs did not specify a comparator of interest.[3-7,9,10,16,18,20] Five SRs sought to include studies with non-PSMA radioligand comparators and other imaging modalities. Tan et al. (2020) examined comparative evidence for 18F-fluciclovine PET/CT imaging,[17] Santhianathen et al. examined comparative evidence for ^{11}C-Choline PET/CT imaging,[8] Moghul et al. and Treglia et al., (2019 (2)) examined comparative evidence for radiolabeled choline PET/CT,[11,19] and Zhou et al. compared PSMA PET/CT to radiolabeled choline PET/CT, ^{18}F-NaF PET/CT, MRI, and bone scintigraphy.[21] With regard to a reference standard for determining diagnostic accuracy 12 SRs specified that any reference standard be used,[3-6,9,16-21] two SRs required a histopathological reference standard,[7,10] and two SRs did not specify a reference standard.[11,12] The different interventions encompassed by PSMA PET was a possible cause of some of the inconsistent overlap of relevant primary study evidence between the included SRs (see Appendix 5).

The guidelines from AUA/ASTRO/SUO included recommendations on a broad range of interventions including first- and second-line antiandrogens, immunotherapy, chemotherapy, radiation therapy, surgery, radiopharmaceuticals, and surveillance strategies. The guidelines considered PET/CT to be an emergent technology while CT, MRI, and bone scan were considered conventional. The authors state that for the purposes

of the recommendations metastatic disease should be identified using conventional imaging.[22,23]

Outcomes

The primary outcomes of the economic analysis were health system costs and survival in years of life over 10 years.[1]

A subset of the diagnostic accuracy outcomes reported by the included SRs were relevant to the inclusion criteria of this report. The sensitivity and specificity of PSMA PET imaging for advanced prostate cancer was reported by eight SRs.[4,7-10,12,20,21] The positive and negative likelihood ratio, LR+ and LR- respectively, were reported by three SRs.[4,7,8] The disease detection rate was reported by ten of the included SRs,[3,4,6,11,12,16-20] while the diagnostic odds ratio was reported by three SRs.[4,7,8] Both positive predictive value (PPV) and negative predictive value (NPV) were reported by two SRs.[4,10]

The included guidelines sought to formulate recommendations using evidence for outcomes of overall survival (OS), prostate cancer mortality, progression-free survival (PFS), PSA progression-free survival, failure-free survival, metastases-free survival, time to metastases, time to progression, skeletal events, and adverse events. For strength of evidence assessments, the guideline development group focused on OS and PFS. Some recommendations also contained consideration for patient preference.

Summary of Critical Appraisal

The economic evaluation of Gordon et al. had significant methodological strengths and a few important limitations. The authors formulated an economically important research question with clear objectives and addressed cost-effectiveness of the intervention with a justified methodological approach and perspective. Sources were provided for both clinical and cost inputs, however the source for the unit cost of the intervention was based on expert opinion and clinical inputs were based on a small (n = 30), single-arm pilot study with limited follow-up. The study used for clinical inputs enrolled a well-defined patient population and examined clearly defined outcomes. The analysis justified the choice of economic model, time horizon, and clearly stated the assumptions made for the model. The authors drew conclusions that followed from the results of the analysis and included the appropriate caveats. This Australian study however may not be generalizable to all healthcare settings especially with respect to usual care and the publication did not provide a conflict of interest (COI) statement. The authors argued that the theme of cost savings through prevention of non-beneficial treatments and the gain in life years should apply outside Australia.[1]

Collectively the body of evidence identified in this report consisting of 16 SRs that examined the diagnostic accuracy of PSMA PET imaging had significant methodological strengths. All SRs conducted a comprehensive systematic literature search.[4-6,10-12,17,20] Defined inclusion and exclusion criteria for literature selection were provided by 14 SRs,[3,5-12,16-21] the selection of which was conducted by more than one reviewer in 13 of those SRs.[3,5-12,16,18-21] Twelve SRs specifically stated that the PRISMA statement was followed while conducting the SR,[3,5,7-11,16-20] and 13 SRs provided a PRISMA flowchart of the literature selection.[3,5-10,16-21] QUADAS-2, a critical appraisal criteria specific to diagnostic studies, was used by 14 of the 16 SRs to appropriately to assess risk of bias of included studies,[3,5-11,16-21] while two of SRs did not conduct a critical appraisal.[4,12] Results of the QUADAS-2 critical appraisals of the studies included in the SRs were summarized by the authors or can be summarized

here as being of overall satisfactory quality,[3,20] a high risk of bias in almost all included studies,[5,6] significant biases in most included studies,[10] low risk of bias overall with higher risks associated with reference standard,[7,17-19] low quality of evidence due to bias of individual results and inconsistency,[11] moderate risk of bias,[9] at high risk of bias primarily due to limitations pertaining to the reference standard,[8,21] or it was not possible to generalize about the body of evidence assessed using QUADAS-2.[16] A total of 261 of the 311 primary study citations, including the overlapping citations, can therefore be summarized as having a potential risk of bias as evaluated by QUADAS-2. Data extraction methodology was provided by 14 SRs,[3,5-11,16-21] and data extraction was performed by more than one reviewer in eight of these SRs.[6-8,10,11,16,17,21] Statistical methodology including a test of statistical heterogeneity was provided by 13 SRs,[3,6-11,16-21] six of which provided some methodology or discussion to account for the identified heterogeneity of the included studies.[3,6,11,16,17,19] All SRs that tested for heterogeneity identified high statistical heterogeneity that was attributed to patient population,[3,8-10,16-20] methodology of PET imaging protocols and equipment,[5,7-9,16-20] combination of different PSMA radioligands,[3,17] and/or inconsistency with regard to the reference standard.[16] Tabulated characteristics of included studies were provided by 15 SRs,[3-11,16-21] and 13 SRs had some discussion of the methodological and evidence limitations of the study.[3-5,7-11,16-20] Five protocols of included SRs were published in the international prospective register of systematic reviews (PROSPERO) prior to being conducted in an attempt to reduce bias.[3,7,8,10,17] Publication bias was assessed by nine of the included SRs,[3,6,7,16-21] and 11 of the SRs had a statement that the authors had no potential COIs.[3,4,6-8,11,12,16,18-20] Significant evidence of publication bias was identified in four SRs in favour of positive results,[3,6,16,17] while evidence for publication bias did not reach significance in five of the included SRs.[7,18-21] None of the SRs described or provided tabulated characteristics of studies that were excluded.[3-12,16-21] Eight SRs did not have a clearly formulated research question,[4-7,10,12,18,20] and seven reported a potential COI.[5,9,10,17,21] Additionally the majority of evidence in the SRs was reportedly derived from retrospective observational studies and the authors of seven of the SRs stated that additional prospective controlled studies would have provided more clarity to the body of evidence.[4,5,7,10,16-18] Annunziata et al. was unique in that it was an SR of MAs and had some less common limitations compared to the other SRs included in this report, namely, it provided no methodology for study selection, no methodology for data extraction, no critical appraisal, and no assessment of overlapping evidence in the included MAs.[4] One SR included a network MA in addition to a direct MA. The network MA enabled comparison between PET radiotracers that were not compared directly in primary studies. The methodology reported for the network analysis aspect of the SR provided limited details. The authors employed a random effects model and assessed heterogeneity of the whole network, within designs, and between designs.[3]

Guidelines developed by AUA/ASTRO/SUO were assessed using AGREE II.[15,22,23] While the overall objectives and patient population of interest were specifically described, the broad focus of the guidelines lacked a specific health question. There was appropriate stakeholder involvement in these guidelines, however the target users of the recommendations were not clearly defined. The methodology for the development of these guidelines described a systematic evidence search with clear selection criteria, methods of recommendation formulation, consideration for benefits and risks, an explicit link between the recommendations and the supporting evidence, and an external guideline review by experts prior to publication. The guideline however did not clearly describe limitations of the body of evidence used or provide a procedure for updating the guidelines. While the recommendations were specific, unambiguous, and clearly identifiable they were unclear as

to different management options. Regarding applicability these guidelines were limited by a lack of information on application, resource implications, and criteria for monitoring implementation. The guidelines were also unclear as to the influence of funding, or if competing interests of the guideline development group were addressed. Potential financial COIs were disclosed.[22,23]

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3.

Summary of Findings

Cost-Effectiveness

The economic analysis of Gordon et al. estimated that over 10 years using ^{68}Ga-PSMA-11 PET/MRI to detect prostate cancer recurrence would cost an average of US$39,426 as compared to usual care costs of US$44,667. In addition, while ^{68}Ga-PSMA-11 PET/MRI produced 7.48 life years compared to 7.41 life years for usual care over 10 years, the higher DR of ^{68}Ga-PSMA-11 PET/MRI resulted in higher treatment costs. This model resulted in an incremental cost per life year saved of US$76,531 with a 95% confidence interval that spanned no difference in cost (US$673,341 savings to US$379,317 in more expenses). The likelihood that ^{68}Ga-PSMA-11 PET/MRI was cost-effective was 87% when a threshold of US$34,626 per life year gained was used. Notably the authors point out that the most important driver of the model was the percentage of patients where ^{68}Ga-PSMA-11 PET/MRI detected prostate cancer lesions. The authors used a DR of 61% for ^{68}Ga-PSMA-11 PET/MRI and a DR of 22% for usual care imaging.[1] One SR included in this review reported a DR for ^{68}Ga-PSMA-11 PET/MRI in an MA that calculated an overall DR of 76%, however this decreased to 38% in patients with BCR of prostate cancer and PSA levels below 0.19 ng/mL.[20]

Diagnostic Accuracy of PSMA PET

Sensitivity and Specificity

The sensitivity and specificity of PSMA PET imaging for advanced prostate cancer was reported by nine of the included SRs.[4,5,7-10,12,20,21] Annunziata et al. reported sensitivity and specificity of from 14 MAs,[4] including three of the SRs included in this report.[7,9,10] Estimates of PSMA PET/CT sensitivity ranged from 0.61 to 0.99 while estimates of specificity ranged from 0.84 to 0.97.[4] Kimura et al. conducted an MA of five studies on ^{68}G-PSMA-11 PET/CT and calculated a sensitivity of 0.84 and a specificity of 0.97 using a lesion-based analysis, and when using a field-based analysis calculated a sensitivity of 0.82 and a specificity of 0.97 in an MA of four studies.[7] Similarly Perera et al. calculated a sensitivity for ^{68}G-PSMA-11 PET/MRI in an MA of five studies of 0.77 per patient and 0.75 per lymph node, and calculated a specificity of 0.97 per patient and 0.99 per lymph node. The authors concluded that ^{68}Ga-PSMA-11 PET appeared to provide superior sensitivity and specificity compared to alternative techniques.[9] In a SR without an MA, Turpin et al., reported a sensitivity and specificity of 0.659 and 0.989 respectively, from a primary study of PSMA PET/CT with 130 patients. In an MA of 298 patients, Turpin et al. reported that PSMA PET/CT had a sensitivity of 0.71 and a specificity of 0.95. In a small primary study of 21 patients PSMA PET/CT had a sensitivity of 0.73 and a specificity of 1.0 in the detection of seminal vesicle invasive prostate cancer, while in another small primary study of 60 patients PSMA PET/CT had a sensitivity of 0.80 and a specificity of 1.0 for the detection of bone metastasis in biological relapse of prostate cancer.[12] Wang et al. conducted a MA of six studies on ^{68}G-PSMA-11 PET/MRI which represented a total of 257 patients and found a per lesion

sensitivity of 0.83 and a per lesion specificity of 0.81.[20] In a narrative systematic review by De Visschere et al. the authors interpreted the evidence of PSMA PET as having very high specificity but moderate sensitivity for lymph node metastasis detection which would imply underestimation of disease load, however this underestimation was less than other PET tracers.[5] Hope et al. conducted a meta-analysis of 15 studies of ^{68}G-PSMA-11 PET which represented a total of 256 patients and reported a sensitivity and specificity of 0.99 and 0.76 respectively. The authors caution that only PSMA-positive lesions were biopsied resulting in a biased low number of true-negative and false-negative lesions.[10] Sathianathen et al. identified a single study reporting a sensitivity of 0.764 and a specificity of 0.998 per lesion for ^{68}G-PSMA-11 PET.[8] In an SR with an MA of 24 studies, Zhou et al., examined the sensitivity and specificity of ^{68}Ga-PSMA-11 PET/CT in the imaging of bone metastases. A per patient sensitivity of 0.97, a per patient specificity of 1.00, and a per lesion sensitivity of 0.88 was calculated and the authors concluded that both PSMA PET/CT and 18F-NaF PET/CT had higher diagnostic value for bone metastasis of prostate cancer than radiolabeled choline PET/CT, MIR, or bone scan.[21] Sensitivity and specificity values for other imaging modalities reported by the included SRs are reported in Appendix 4.

Positive Likelihood Ratio (LR+) and Negative Likelihood Ratio (LR-)

The positive and negative likelihood ratios were reported by three of the included SRs,[4,7,8] however only two SRs reported LR+ and LR- for PSMA PET imaging.[4,7] Annunziata identified four MAs that reported LR+, ranging from 7.91 to 30.0, and LR-, ranging from 0.14 to 0.37.[4] In a lesion-based MA of five studies, Kimura et al. reported a LR+ of 30.3 and a LR- of 0.16, and in a field-based MA of four studies reported a LR+ of 15.8 and a LR- of 0.16.[7]

Positive Predictive Value (PPV) and Negative Predictive Value (NPV)

The PPV and NPV were reported by one SR included in this report.[10] Due to the fact that only PSMA-positive lesions were biopsied potentially biasing to a low number of true-negative and false-negative lesions the authors suggest that the most relevant measure was the PPV, calculated in this MA of 15 studies of ^{68}G-PSMA-11 studies of biochemical recurrent prostate cancer to be 0.99. The NPV was calculated to be 0.76 from the same body of evidence.[10]

Diagnostic Odds Ratio (DOR)

The DOR for PSMA PET was reported by three of the included SRs,[4,7,8] however only two SRs reported a DOR for PSMA PET.[4,7] Annunziata et al. reported a DOR in four MAs that ranged from 29 to 189.[4] In a lesion-based MA of five studies, Kimura et al. reported a DOR of 189, and in a field-based analysis of four studies reported a DOR of 82 for ^{68}G-PSMA-11 PET/CT.[7]

Disease Detection Rate (DR)

A disease detection rate (DR) was reported by 11 of the SRs included in this report.[3-6,11,12,16-20] In both a direct comparison MA and a network MA, Crocerossa et al. compared ^{18}F-FCholine, ^{11}C-Choline, and ^{18}F-FACBC radiotracers with PSMA PET radioligands ^{18}F-PSMA-1007, ^{64}Cu-PSMA-617, ^{68}G-PSMA-11, and ^{18}F-DCFPyL. In a network analysis it was found that ^{18}F-PSMA-1007 had a significantly greater overall positivity as compared to ^{18}F-FCholine (OR [95%CI]: 33% [11% to 94%]). None of the other comparisons (all iterations) demonstrated any statistically significant superiority in detection rates, either between radiolabeled choline PET and PSMA PET, or between different PSMA PET tracers. The network analysis identified a high risk of heterogeneity (P = 0.004) and inconsistency (P =

0.002) in a random effect model.[3] Evangelista et al. reported a DR for PSMA PET/MRI of 81.8% (95%CI: 72.4 to 88.4) and a DR of radiolabeled choline PET/MRI of 77.3% (95%CI: 53.7 to 90.9). Turpin et al. reported DRs from several studies, two of which compared DRs of PSMA PET with other PET imaging tracers. In a study of 123 patients lymph node recurrence was detected in 94% with PSMA PET and 71% with radiolabeled choline PET, and this difference was statistically significant. Another study, identified by Turpin et al. of 50 patients, however reported lymph node recurrence detection of 30% with PSMA PET and 8% with ^{18}F-FCholine PET and the difference was not statistically different. Turpin et al. concluded that while there is prospective evidence of diagnostic superiority of PSMA PET or ^{18}F-Fluciclovine PET to radiolabeled choline PET, further research is required to determine if there is a beneficial impact on patient survival.[12] Detection rates of ^{68}G-PSMA-11 compared to radiolabeled choline PET/CT, were also reported in a MA by Moghul et al. where ^{68}G-PSMA-11 had a statistically significant higher detection rate overall (OR 2.27; 95%CI: 1.06 to 4.85) but not when looking at recurrence with PSA < 2 ng/mL (OR 2.37; 95%CI: 0.61 to 9.17). The lower DR of PSMA PET in patients with BCR of prostate cancer and lower PSA levels was also observed in five SRs included in this report.[5,16-19] Tan et al. calculated a statistically significant greater DR using ^{68}G or ^{18}F-PSMA PET (79.9%; 95%CI: 74.6% to 85.3%) as compared to ^{18}F-FCholine PET (62.1%; 95%CI: 54.5% to 69.6%) in post-treatment patients with a PSA between 1.0 and 1.9 ng/mL, however the difference was not statistically different in post-treatment prostate cancer patients with PSA levels below 1.0 ng/mL.[17] Despite the lower DR for PSMA PET in the context of lower PSA levels in patients with BCR of prostate cancer, one MA (Treglia et al. 2019(2))[19] calculated statistically significant higher detection rate from five pooled studies for PSMA PET/CT as compared to radiolabeled choline PET/CT in patients with PSA less than or equal to 1ng/mL. In this MA, a statistically significant difference was not observed in patients overall or patients with PSA greater than 1ng/mL.[19] Wang et al., also identified a statistically significant increase in DR of ^{68}G-PSMA-11 PET/MRI with increasing PSA levels in patients with BCR of prostate cancer.[20] Two other SRs also concluded that PSMA PET provided higher DR compared to PET with other radiotracers in patients with BCR of prostate cancer and low serum PSA levels.[3-5]

More detailed diagnostic accuracy outcomes of PSMA PET and other diagnostic imaging modalities as well as authors' conclusions reported in the included SRs are provided in Appendix 4.

Guidelines

PSMA PET

The guidelines formulated by the AUA/ASTRO/SUO guideline development group provided one recommendation relevant to PSMA PET imaging for patients with BCR prostate cancer. The recommendation stated that, "Clinicians may utilize novel PET-CT scans (e.g., fluciclovine, choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging." This recommendation was rated as an expert opinion which means that the recommendation may or may not be supported by evidence in the medical literature and was instead achieved by consensus of the guideline development group based on the experience, training, knowledge, and judgement of its members.[22,23]

Limitations

The cost-effectiveness evidence of PSMA PET imaging for BCR of prostate cancer was limited by the quantity of evidence identified and the unclear applicability of the evidence to the Canadian healthcare setting.

The evidence of the diagnostic accuracy of PSMA PET imaging for BCR of prostate cancer was limited by the unknown impact possible publication bias identified by four SRs,[3,6,16,17] and the overlap of primary study evidence in the included SRs (Appendix 5). Additionally, while the quantity of the underlying body of evidence compiled by the included SRs was extensive, the quality, as assessed by 11 of 13 SRs, had potential for bias,[5-8,10,11,16-19,21] most commonly with regard to inconsistent use of reference standard.[7,8,17-19,21] The impact of this bias is unclear. There was limited information on the imaging hardware and software used in the primary studies however only one SR suggested it as a possible source of heterogeneity.[5]

Although the evidence-based guidelines from AUA/ASTRO/SUO were formulated with few methodological limitations, the relevant recommendation regarding PSMA PET imaging for BCR of prostate cancer was based upon expert opinion. The biases associated with the opinion and the reported conflict of interests are unclear as no supporting evidence was cited.

Conclusions and Implications for Decision or Policy Making

One identified study evaluated the cost-effectiveness of PSMA PET imaging for BCR of prostate cancer from the perspective of the Australian healthcare setting.[1] This was a well-conducted study, with the important limitations that it used expert opinion for the cost of the PSMA PET imaging intervention and derived clinical data inputs from a small pilot study. Using a threshold of US$34,626 per life year gained, ^{68}Ga-PSMA-11 PET/MRI was found to be cost-effective relative to the usual care imaging modalities, CT and bone scan. The applicability of this study to the Canadian healthcare setting was unclear, especially with regard to the usual care comparator.

This report identified evidence from 16 SRs,[3-12,16-21] 13 of which included a MA,[3,6-11,16-21] which summarized data from over 200 primary studies on the diagnostic accuracy of PSMA PET imaging for advanced prostate cancer. A total of 67 out of 197 of the relevant primary studies were cited by more than one of the included SRs. Fourteen of the SRs included in this report had important strengths and few methodological limitations,[3,5-11,16-21] however all of the MAs identified high heterogeneity among the included primary studies.[3,6-11,16-21] Critical appraisals from 11 SRs, representing 261 of the total 311 relevant primary study citations including the existing overlap, reported a risk of bias,[5-8,10,11,16-19,21] the most common concern was associated with the reference standard,[7,8,17-19,21] whereas three SRs citing 50 relevant primary studies reported satisfactory or moderate risk of bias overall.[3,9,20] Additionally, evidence for the possibility of publication bias was identified within the body of primary evidence included in four of the nine SRs that assessed publication bias.[3,6,7,16-21] Despite the heterogeneity and a lack of consistent diagnostic performance between the underlying primary studies, a consensus was identified that PSMA PET had useful diagnostic accuracy for patients with advanced prostate cancer in all 16 SRs.[3-12,16-21] Comparative evidence was also identified in seven SRs in which greater PSMA PET diagnostic accuracy than the examined comparators 18F-fluciclovine,[17] ^{11}C-Choline,[8] ^{18}F-FCholine,[3] any radiolabeled choline-based PET/CT,[11,12,19,21] ^{18}F-NaF PET/CT,[21] MRI,[21] and

bone scan[21] was reported. Of these comparisons statistically significant differences in diagnostic accuracy outcomes favouring PSMA PET were observed in comparisons of ^{18}F-PSMA-1007 to ^{18}F-FCholine PET/CT,[3] ^{68}G-PSMA-11 as compared to radiolabeled choline PET/CT,[11] ^{68}G or ^{18}F-PSMA compared to ^{18}F-fluciclovine,[17] and PSMA PET/CT compared to radiolabeled choline PET/CT.[12,19] One MA found no statistically significant differences between different PSMA PET radioligands.[3] A consensus that the diagnostic accuracy of PSMA PET decreases with decreasing PSA levels in BCR of prostate cancer patients was also identified.[3,5,9,16-20] This correlation of PET imaging diagnostic accuracy with PSA levels was also observed in other PET tracers however, and PSMA PET was found to have significantly better diagnostic accuracy in patients with BCR of prostate cancer and PSA levels less than or equal to 1ng/mL in one MA.[19] Authors conclusions reported a consensus that larger well-designed prospective studies using a well-defined reference standard are required to better define the improved diagnostic performance, the impact of improved diagnostic accuracy on patient-related outcomes, and cost-effectiveness of PSMA PET imaging for BCR of prostate cancer.[4,5,7,10,16-18]

One evidence-based guideline, from AUA/ASTRO/SUO was identified that included a recommendation specific to PSMA PET imaging for BCR of prostate cancer. It is recommended that clinicians may use novel PET/CT scans including PSMA PET/CT for patients with BCR of prostate cancer after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging. Conventional imaging was defined as CT, MRI, and bone scan and novel PET/CT did not distinguish between PSMA PET/CT, ^{18}F-Fluciclovine, or radiolabeled choline PET/CT. This recommendation was based upon the expert opinion of the guideline development group, and no relevant supporting evidence for this recommendation was cited.[22,23]

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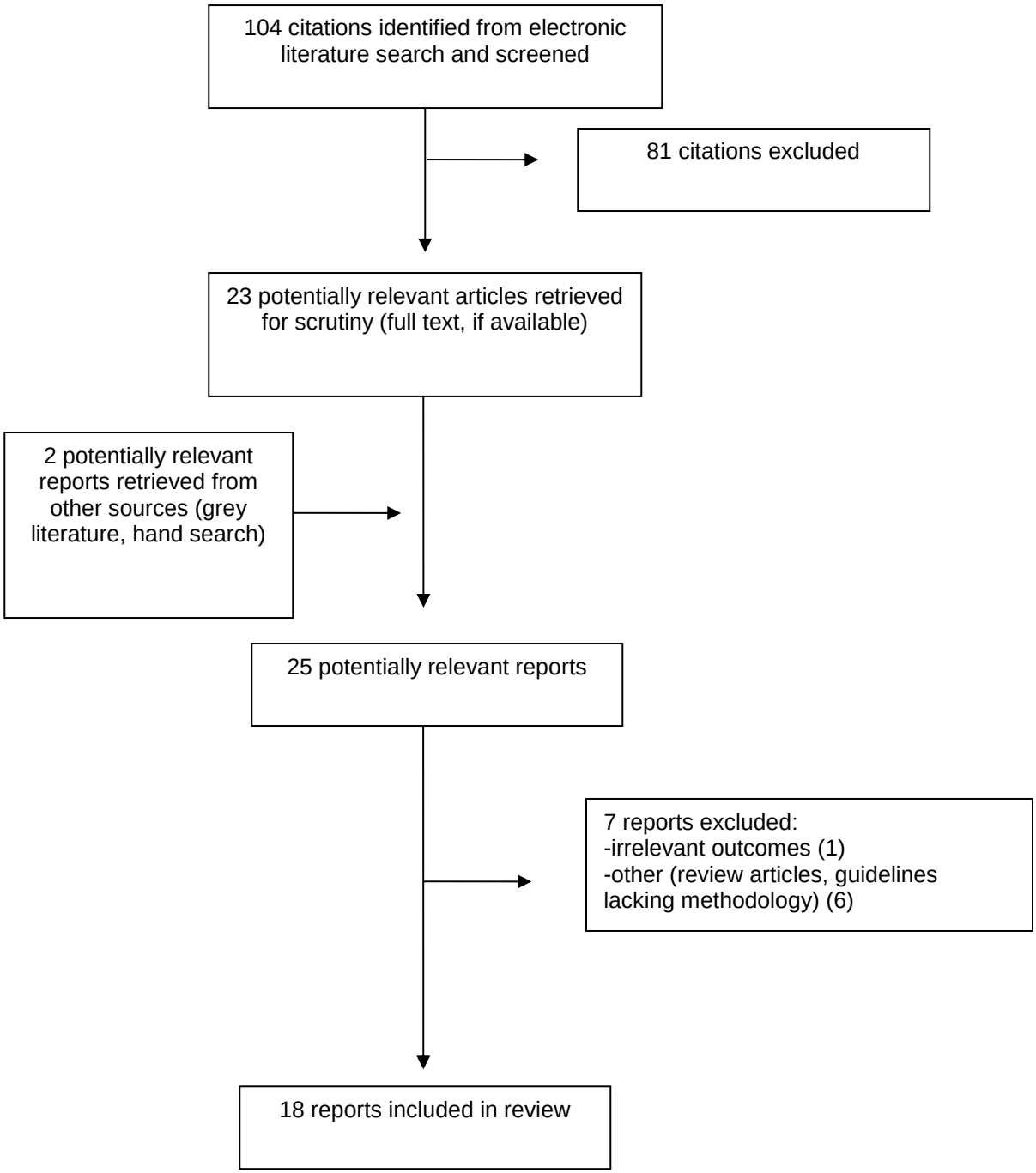
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Economic Evaluation

Study citation country, funding source	Type of analysis, time horizon, perspective	Population characteristics	Intervention and comparator(s)	Approach	Source of clinical, cost, and utility data used in analysis	Main assumptions
Gordon et al., (2020),[1] Australia. **Prostate Cancer Foundation of Australia's Research Program**	Exploratory cost-effectiveness analysis, with a ten-year time horizon, from the perspective of the Australian health system	Patients with BCR of prostate cancer after primary curative treatment. BCR defined as PSA > 0.2 ng/mL on at least two occasions post surgery or PSA ≥ 2.0 ng/mL over nadir two years post radiotherapy.	Compared to usual care: typically involved a bone scan and MRI	Decision-analytic model with Markov chains with a ten-year duration and annual cycles.	Clinical data derived from PSMA PET/MRI Biochemical Recurrence Trial, the Australian Medicare costing schedules were used to inform costs, a threshold of US$34 626 per life year gained used as a benchmark	False positives were expected to survive with local disease expectations. False negatives received localized treatment but with survival expectations of nodal or distant cancer.

BCR = biochemical recurrence; MRI = magnetic resonance imaging; PET = positron emission tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

Table 3: Characteristics of Included Systematic Reviews and Network Meta-Analyses

Study citation, country, Funding: source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Annunziata et al., (2020),[4] Switzerland. **No external Funding**	SR of 39 MAs	Patients with prostate cancer	PET imaging Any reference standard	• Sensitivity • Specificity • LR+ • LR- • DOR • DR
Crocerossa et al., (2020),[3] US and Italy. **No external Funding**	SR of 43 studies with MA of 34 of the included studies (authors reported that most studies were retrospective)	Patients with BCR of prostate cancer	PSMA PET/CT Any reference standard	• DR
Evangelista et al., (2020),[6] Italy. **No external Funding**	SR with MA that included 50 studies (20 prospective, 30 retrospective)	Patients with prostate cancer	PET/MRI Any reference standard	• DR
Kimura et al., (2020),[7] Austria, Japan.	SR with MA of 14 nonrandomized	Patients with BCR of prostate cancer following primary local	PSMA PET	• Sensitivity • Specificity • LR+

Study citation, country, Funding: source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding: not reported	retrospective observational studies	therapy with curative intent	Histopathologic reference standard	● LR- ● DOR
Perera et al., (2020),[9] Australia. **Funding: includes scholarships and clinician awards**	SR with MA of 37 studies (authors reported that the majority were retrospective, single-center studies)	Patients with prostate cancer	^{68}Ga PSMA PET Any reference standard	● Sensitivity ● Specificity
Tan et al., (2020),[17] US. **Funding: not reported**	SR with MA of 44 studies (authors reported that most studies were retrospective analyses)	Patients with BCR of prostate cancer following definitive therapy	^{68}Ga or ^{18}F PSMA PET/CT ^{18}F-Fluciclovine PET/CT Any reference standard	● DR
Turpin et al., (2020),[12] France. **Funding: not reported**	SR of 105 articles (authors reported 16 reviews, 5 MAs, 11 guidelines or position statements, and 73 primary studies)	Patients with metastatic prostate cancer	Any imaging	● Sensitivity ● Specificity ● DR
Wang et al., (2020),[20] China. **Funding: Key Projects of the Ministry of Science and Technology**	SR with MA of 13 studies (authors reported that all were retrospective single-center studies)	Patients with primary or BCR of prostate cancer	^{68}Ga PSMA PET/MRI Any reference standard	● Sensitivity ● Specificity ● DR
De Visschere et al., (2019),[5] Belgium. **Funding: not reported**	SR of 98 studies (authors reported that most studies were retrospective)	Patients with recurrent prostate cancer	Any imaging Any reference standard	● Sensitivity ● Specificity ● DR
Hope et al., (2019),[10] US. **Funding: Prostate Cancer Foundation and the National Institutes of Health**	SR with MA of 41 studies (authors reported that four of these studies were prospective)	Patients with BCR of prostate cancer	^{68}Ga PSMA PET Histopathology as gold standard	● Sensitivity ● Specificity ● PPV ● NPV
Moghul et al., (2019),[11] UK.	SR of 3 studies (all studies were observational	Patients with recurrent prostate cancer	PSMA PET/CT compared to	● DR ● Adverse side effects

Study citation, country, Funding: source	Study designs and numbers of primary studies included	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
No external Funding	comparative studies, one of which was prospective)		radiolabeled choline PET/CT	
Sathianathen et al., (2019),[8] US. **Funding: Cloverfields Foundation and The Institute for Prostate and Urologic Cancers**	SR with MA of 21 studies (three of these studies were prospective)	Patients with BCR of prostate cancer	PET/CT using ^{18}F-FACBC, ^{68}Ga-PSMA-11, or ^{11}C-Choline Pathology, further imaging, and/or clinical course as a reference standard	● Sensitivity ● Specificity ● LR+ ● LR- ● DOR
Tan et al., (2019),[16] US. **Funding: University of California-Riverside School of Medicine Summer Fellowship Program**	SR with MA of 43 studies (authors reported that most studies were retrospective)	Patients with BCR of prostate cancer following definitive therapy	PSMA PET Any reference standard	● DR
Treglia et al., (2019),[18] Switzerland. **No external Funding**	SR of 15 studies with MA of 6 of the included studies (authors reported that most studies were retrospective)	Patients with BCR of prostate cancer	^{18}F PSMA PET/CT Any reference standard	● DR
Treglia et al., (2019),[19] Switzerland. **Funding: not reported**	SR of 10 studies with MA of 5 studies (authors reported that most studies were retrospective)	Patients with BCR of prostate cancer	PSMA PET/CT compared to radiolabeled choline PET/CT Any reference standard	● DR
Zhou et al., (2019),[21] China. **Funding: not reported**	SR with MA of 24 studies (12 prospective studies, 9 retrospective studies, and 3 clinical controlled studies)	Patients with prostate cancer metastasized to bone	PSMA PET/CT, radiolabeled choline PET/CT, ^{18}F-NaF PET/CT, MRI, and bone scintigraphy Any reference standard	● Sensitivity ● Specificity

BCR = biochemical recurrence; CT = computed tomography; DOR = diagnostic odds ratio; DR = disease detection rate; FN = false negative; FP = false positive; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MA = metanalysis; MRI = magnetic resonance imaging; PET = positron emission tomography; PPV = positive predictive value; PSMA = prostate-specific membrane antigen; SR = systematic review; TN = true negative; TP = true positive

Table 4: Characteristics of Included Guideline

Intended users, target population	Intervention and practice considered	Major outcomes considered	Evidence collection, selection, and synthesis	Evidence quality assessment	Recommendations development and evaluation	Guideline validation
AUA/ASTRO/SUO Guidelines, 2020[22,23]						
Intended users: Clinicians **Target population: Patients with diagnosis of advanced prostate cancer**	Broad consideration of interventions: first- and second-line antiandrogens, immunotherapy, chemotherapy, radiation therapy, surgery, radiopharmaceuticals, and surveillance strategies	Overall survival (OS), prostate cancer mortality, progression-free survival (PFS), prostate-specific antigen progression-free survival (PSA-PFS), failure-free survival, metastases-free survival, time to metastases, time to progression, skeletal events, and adverse events	Systematic Review of RCTs, PICO for inclusion and exclusion criteria, evidence tables with study characteristic, results, and risk of bias along with summary tables of main findings.	Assessed in duplicate using criteria from US Preventative Services Task Force Evidence Strength Rated A - Well conducted RCTs or consistent findings from exceptionally strong observational studies B - RCTs with methodological limitations or generalizability or moderately strong observational studies. C-RCTs with serious limitations or inconsistent observational studies	Recommendation formulation methodology not reported. Recommendations were graded using AHRQ EPC Methods Guide for Comparative Effectiveness and Effectiveness Reviews Recommendations graded Strong - Benefits are greater than the risk/burden and applies to most patients in most circumstances Moderate - Net benefit (or net harm) is moderate Conditional - The best action is dependent on the individual patient Clinical Principle - a component of care broadly agreed upon that may not have supporting evidence Expert Opinion - Guideline panel consensus that may not have supporting evidence	Reviewed by internal and external peer review. Also sought patient perspective

ASTRO = American Society for Radiation Oncology; AUA = American Urological Association; SUO = Society of Urologic Oncology

Appendix 3: Critical Appraisal of Included Publications

Table 5: Strengths and Limitations of Economic Evaluation Using the Drummond Checklist[14]

Strengths	Limitations
Gordon et al., 2020[1]	
● Research question of economic importance was formulated ● Methodological approach and perspective were justified ● Clinical and cost inputs sources provided ● Objectives and outcomes clearly stated ● Well defined patient population ● Cost data inputs sourced and currency conversions provided ● Choice of model justified ● Time horizon stated ● Sensitivity analyses undertaken ● Discount rate stated ● Model assumptions clearly stated ● Conclusions follow from data with appropriate caveats	● Clinical inputs based on small single-arm study with limited follow-up ● Usual care intervention may not be generalizable to all healthcare settings ● No COI statement ● Source for unit cost of intervention of interest was expert opinion

COI = conflict of interest

Table 6: Strengths and Limitations of Systematic Reviews and Network Meta-Analyses Using AMSTAR 2[13]

Strengths	Limitations
Annunziata et al., (2020)[4]	
● Comprehensive systematic literature search performed ● A table of limited study characteristics provided ● A discussion of limitations provided ● Statement of no COIs	● No methodology for study selection or data extraction ● Reasons not provided for excluded studies ● Table of excluded SRs not provided ● Study questions not clear (not formulated using PICO) ● Limited information on inclusion and exclusion criteria ● No critical appraisal with a brief discussion on risk of bias ● No assessment of publication bias ● Limited quantified synthesis of evidence ● No assessment or accounting of overlap between included SRs
Crocerossa et al., (2020)[3]	
● Comprehensive systematic literature search ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Prospectively registered systematic review methodology (PROSPERO) ● PICO formulated research question ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Statistical methodology described and tested heterogeneity prior to inclusion of studies in MA ● Data extraction methodology provided ● Publication bias analyzed appropriately ● A table of limited study characteristics provided	● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies

Strengths	Limitations
● A discussion of limitations provided ● Statement of no COIs	
Evangelista et al., (2020)[6]	
● Comprehensive systematic literature search performed ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Provided PRISMA flowchart of literature selection ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Statistical methodology described and tested and accounted for heterogeneity ● Publication bias analyzed appropriately ● A table of limited study characteristics provided ● Data extraction performed in duplicate ● Statement of no COIs	● Research question not clearly defined ● Table of excluded studies not provided ● Narrow discussion of study limitations ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Kimura et al., (2020)[7]	
● Comprehensive systematic literature search performed ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Prospectively registered systematic review methodology (PROSPERO) ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● A table of limited study characteristics provided ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Statistical methodology described and tested heterogeneity ● Publication bias analyzed appropriately ● Data extraction performed in duplicate ● A discussion of limitations provided ● Statement of no COIs	● Research question not clearly defined ● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Perera et al., (2020)[9]	
● Comprehensive systematic literature search performed ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● A table of limited study characteristics provided ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Statistical methodology described and tested heterogeneity ● Data extraction methodology provided ● A discussion of study limitations provided	● Reported potential COI ● Table of excluded studies not provided ● No assessment of publication bias ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Tan et al., (2020)[17]	
● Comprehensive systematic literature search ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Prospectively registered systematic review methodology (PROSPERO)	● Reported potential COI ● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies

Strengths	Limitations
● Critical appraisal performed using standard risk assessment tool (QUADAS-2) ● Literature selection performed using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Statistical methodology described and tested and accounted for heterogeneity ● Publication bias analyzed appropriately ● Data extraction performed in duplicate ● A discussion of study limitations provided	
Turpin et al., (2020)[12]	
● Comprehensive systematic literature search ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Statement of no potential COIs	● Research question broad and not clearly defined ● No data extraction methodology ● Characteristics of all included studies not provided ● Reasons not provided for excluded studies ● Table of excluded studies not provided ● No critical appraisal ● No assessment of publication bias ● Narrow discussion on study limitations provided
Wang et al., (2020)[20]	
● Comprehensive systematic literature search ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Statistical methodology described and tested heterogeneity ● Publication bias analyzed appropriately ● Data extraction methodology provided ● Statement of no potential COIs ● A discussion of study limitations provided	● Research question broad and not clearly defined ● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
De Visschere et al., (2019)[5]	
● Comprehensive systematic literature search ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Data extraction methodology provided ● A table of limited study characteristics provided ● A discussion of study limitations provided	● Research question broad and not clearly defined ● Table of excluded studies not provided ● No assessment of publication bias ● Reported potential COIs
Hope et al., (2019)[10]	
● Comprehensive systematic literature search ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Literature selection performed in duplicate using defined inclusion and exclusion criteria	● Research question not clearly defined ● Table of excluded studies not provided ● No assessment of publication bias ● Reported potential COI

Strengths	Limitations
● A table of limited study characteristics provided ● Prospectively registered systematic review methodology (PROSPERO) ● Critical appraisal performed using standard risk assessment tool (QUADAS-2) ● Data extraction performed in duplicate ● Statistical methodology described and tested heterogeneity ● A discussion of study limitations provided	● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Moghul et al., (2019)[11]	
● Comprehensive systematic literature search ● Followed PRISMA statement ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Critical appraisal performed using standard risk assessment tool (QUADAS-2) ● Data extraction performed in duplicate ● Statistical methodology described and tested and accounted for heterogeneity ● Statement of no potential COIs ● A discussion of study limitations provided	● Table of excluded studies not provided ● No assessment of publication bias ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Sathianathen et al., (2019)[8]	
● Comprehensive systematic literature search performed ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Prospectively registered systematic review methodology (PROSPERO) ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Statistical methodology described and tested heterogeneity ● Statement of no potential COIs ● Data extraction performed in duplicate ● A discussion of study limitations provided	● Table of excluded studies not provided ● No assessment of publication bias ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Tan et al., (2019)[16]	
● Comprehensive systematic literature search performed ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● A table of limited study characteristics provided ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Publication bias analyzed appropriately ● Statistical methodology described and tested and accounted for heterogeneity ● Statement of no potential COIs ● Data extraction performed in duplicate ● A discussion of study limitations provided	● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies

Strengths	Limitations
Treglia et al., (2019)[18]	
● Comprehensive systematic literature search performed ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Publication bias analyzed appropriately ● Statistical methodology described and tested heterogeneity ● Statement of no potential COIs ● Data extraction methodology provided ● A discussion of study limitations provided	● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies ● Research question not clearly defined
Treglia et al., (2019)[19]	
● Comprehensive systematic literature search performed ● Followed PRISMA statement ● Provided PRISMA flowchart of literature selection ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Publication bias analyzed appropriately ● Statistical methodology described and tested and accounted for heterogeneity ● Statement of no potential COIs ● Data extraction methodology provided ● A discussion of study limitations provided	● Table of excluded studies not provided ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies
Zhou et al., (2019)[21]	
● Comprehensive systematic literature search performed ● Provided PRISMA flowchart of literature selection ● Literature selection performed in duplicate using defined inclusion and exclusion criteria ● A table of limited study characteristics provided ● Critical appraisal performed in duplicate using standard risk assessment tool (QUADAS-2) ● Statistical methodology described and tested heterogeneity ● Statement of no potential COIs ● Data extraction performed in duplicate ● A discussion of study limitations provided	● Not enough data to assess publication bias ● Reasons not provided for excluded studies ● Significant statistical heterogeneity (I^2 > 75%) in MA of pooled studies

AMSTAR 2 = A MeaSurement Tool to Assess systematic Reviews 2; COI = conflict of interest; PRISMA = Preferred Reporting Items for a Systematic Review and Meta-Analysis; PROSPERO = International Prospective Register of Systematic Reviews database; QUADAS-2 = Qualtiy Assessment of Diagnostic Accuracy Studies

Table 7: Strengths and Limitations of Guideline Using AGREE II[15]

Item	Guideline
	AUA/ASTRO/SUO Guidelines, 2020[22,23]
Domain 1: Scope and Purpose	
1. The overall objective(s) of the guideline is (are) specifically described.	Yes
2. The health question(s) covered by the guideline is (are) specifically described.	No
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Yes
Domain 2: Stakeholder Involvement	
4. The guideline development group includes individuals from all relevant professional groups.	Yes
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Yes
6. The target users of the guideline are clearly defined.	No
Domain 3: Rigour of Development	
7. Systematic methods were used to search for evidence.	Yes
8. The criteria for selecting the evidence are clearly described.	Yes
9. The strengths and limitations of the body of evidence are clearly described.	No
10. The methods for formulating the recommendations are clearly described.	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Yes
12. There is an explicit link between the recommendations and the supporting evidence.	Yes
13. The guideline has been externally reviewed by experts prior to its publication.	Yes
14. A procedure for updating the guideline is provided.	No
Domain 4: Clarity of Presentation	
15. The recommendations are specific and unambiguous.	Yes
16. The different options for management of the condition or health issue are clearly presented.	Unclear
17. Key recommendations are easily identifiable.	Yes
Domain 5: Applicability	
18. The guideline describes facilitators and barriers to its application.	No
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	No
20. The potential resource implications of applying the recommendations have been considered.	No

Item	Guideline
	AUA/ASTRO/SUO Guidelines, 2020[22,23]
21. The guideline presents monitoring and/or auditing criteria.	No
Domain 6: Editorial Independence	
22. The views of the funding body have not influenced the content of the guideline.	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Unclear

AGREE II = Appraisal of Guidelines for Research and Evaluation II

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings of Included Economic Evaluation

Main study findings	Authors' conclusion
Gordon et al., 2020[1]	
10-year model duration (base case) **Mean cost (US$)** ^{68}Ga-PSMA-11 PET/MRI $56,961 Usual Care $64,449 Mean difference (95% CI) -$5,258 (-17,206 to 5,419) **Mean life years** ^{68}Ga-PSMA-11 PET/MRI 7.48 Usual Care 7.41 Mean difference (95% CI) 0.069 (-0.006 to 0.163) **Incremental cost per life year saved (US$ (95% CI))** -$76,531 (-673,341 to 379,317) 87% likelihood of cost-efficacy of ^{68}Ga-PSMA-11 PET/MRI **5-year model duration** **Mean cost (US$)** ^{68}Ga-PSMA-11 PET/MRI $28,311 Usual Care $30,581 Mean difference (95% CI) -$2,270 (-9855 to 4549) **Mean life years** ^{68}Ga-PSMA-11 PET/MRI 4.34 Usual Care 4.32 Mean difference (95% CI) 0.018 (-0.005 to 0.046) **Incremental cost per life year saved (US$ (95% CI))** -$186,632 (-702,732 to 392,727) An incremental cost-effectiveness scatterplot of 1000 iterations shows the majority of incremental cost and incremental life year pairings were cost saving with ^{68}Ga-PSMA-11 PET/CT as compared to usual care. A total of 87% of simulations indicated that ^{68}Ga-PSMA-11 PET/CT would be cost-effective at the US$34,626 per life year saved threshold.	"How these disruptive technologies improve patient outcomes is also yet to be determined and will require ongoing investigation. This current study however, does support from a health economic analysis perspective in the BCR setting in the Australian health system, the use of 68Ga-PSMA-11 PET/MRI as a cost effective replacement for the usual CT and Bone Scan staging scans." (page 312) "The most important driver of the model was the percentage of patients where ^{68}Ga-PSMA-11 detected prostate cancer lesions." (page 307)

CI = confidence interval; PET/CT = positron emission tomography/computed tomography; PSMA = prostate-specific membrane antigen

Table 9: Summary of Findings Included Systematic Reviews and Network Meta-Analyses

Main study findings							Authors' conclusion
Annunziata et al., (2020)[4]							
PSMA PET/CT MA	**Se**	**Sp**	**LR+**	**LR-**	**DOR**	**DR(%)**	"Evidence-based data showed the good diagnostic performance of PET imaging with several radiopharmaceuticals in different PCa clinical settings, including staging and restaging. In BR-PCa patients with low serum PSA values, PET with PSMA-targeted agents seems to provide a higher detection rate compared to PET with other radiopharmaceuticals. More prospective multicentric studies and cost-effectiveness analyses are warranted." (p. 11) "All the meta-analyses here discussed showed an increasing interest about the role of PET/CT with PSMA-targeted agents due to their good diagnostic performance in several clinical settings of PCa" "Despite these clear evidences, PSMA-targeted agents are still classified as experimental radiopharmaceuticals in several countries at the moment, and this has an influence on the use of these PET radiopharmaceuticals in the clinical practice." (page 10)
Tan et al., 2020[17]	NA	NA	NA	NA	NA	NA	
Kimura et al., 2020[7]	0.84	0.97	30.3	0.16	189	NA	
Wu et al., 2020	0.65	0.94	10.6	0.37	29	NA	
Perera et al., 2020[9]	0.77	0.97	NA	NA	NA	NA	
Tan et al., 2019[21]	NA	NA	NA	NA	NA	70	
Treglia et al., 2019[18]	NA	NA	NA	NA	NA	78	
Lin et al., 2019	0.92	0.94	7.91	0.14	79.04	NA	
PereriaMestre et al., 2019	NA	NA	NA	NA	NA	72	
Hope et al., 2019[10]	0.74/0.99	0.96/0.76	NA	NA	NA	NA	
Kim et al., 2019	0.71	0.95	15.6	0.30	51	NA	
Han et al., 2018	NA	NA	NA	NA	NA	NA	
Von Eyben et al., 2018	0.61-0.7	0.84-0.97	NA	NA	NA	74	
Von Eyben et al., 2018	0.87-0.93	0.93-1	NA	NA	NA	81	
Perera et al., 2016	0.86	0.86	NA	NA	NA	40/76	
Choline PET/CT MA	**Se**	**Sp**	**LR+**	**LR-**	**DOR**	**DR(%)**	
Kim et al., 2019	0.57	0.94	10.2	0.46	22	NA	
Treglia et al., 2019[22]	NA	NA	NA	NA	NA	56	
Zhou et al., 2019[21]	0.87	0.99	NA	NA	504	NA	
Lin et al., 2019	0.93	0.83	4.98	0.10	68.27	NA	
Sathianathen et al., 2019[8]	0.81	0.84	5.4	0.24	25.2	62	
Guo et al., 2018	0.89	0.98	40.4	0.12	344	NA	
Wei et al., 2018	0.82	0.92	6.61	0.20	38.55	59	
Evangelista et al., 2016	0.85	0.33	1.21	0.46	2.83	NA	
Liu et al., 2016	0.76-0.83	0.82-0.93	4.5-11.7	0.21-0.26	22-46	NA	
Von Eyben et al., 2016	NA	NA	NA	NA	NA	55	
Fanti et al., 2016	0.89	0.89	NA	NA	NA	62	
Ouyang et al., 2016	0.73-0.78	0.79-0.90	NA	NA	NA	NA	
Shen et al., 2014	0.91	0.99	NA	NA	150.70	NA	
Treglia et al., 2014	NA	NA	NA	NA	NA	58	
Von Eyben et al., 2014	0.59	0.92	6.86	0.45	19.17	NA	
Umbehr et al., 2013	0.84/0.85	0.79/0.88	4.02/7.06	0.2/0.17	20.4/41.4	NA	
Evangelista et al., 2013	0.86	0.93	NA	NA	62.12	NA	
Evangelista et al., 2013	0.49	0.95	8.35	0.55	18.99	NA	
Fluciclovine PET/CT MA	**Se**	**Sp**	**LR+**	**LR-**	**DOR**	**DR(%)**	
Tan et al., 2020[17]	NA	NA	NA	NA	NA	NA	
Bin etl a., 2020	0.88	0.73	3.3	0.17	20	NA	
Laudicella et al., 2019	0.86	0.76	4.5	0.34	16.4	NA	
Kim et al., 2019	0.56-0.87	0.84-0.98	5.3-19.3	0.16-0.48	34-44	NA	
Kim et al., 2019	0.79	0.69	2.5	0.3	9	NA	
Sathianathen et al., 2019[8]	0.8	0.62	2.1	0.36	8	59	
Ren et al., 2016	0.87	0.66	NA	NA	NA	NA	
Acetate PET/CT MA	**Se**	**Sp**	**LR+**	**LR-**	**DOR**	**DR(%)**	
Liu et al., 2016	0.79	0.59	1.9	0.35	6	NA	
Ouyang et al., 2014	0.79	0.59	NA	NA	NA	NA	
Mohsen et al., 2013	0.75/0.64	0.76/0.93	1.8	0.45	3.9	NA	
Fluoride PET/CT MA	**Se**	**Sp**	**LR+**	**LR-**	**DOR**	**DR(%)**	
Zhou et al., 2019[21]	0.96	0.97	NA	NA	674	NA	

Main study findings							Authors' conclusion
Sheikhbahaei et al., 2019	0.98	0.92	6.6	0.07	123.2	NA	
Crocerossa et al., (2020)[3]							
Overall positivity RR (95%CI) - Direct comparison meta-analysis (RR < 1 favours PSMA) **^{18}F-PSMA-1007** vs ^{18}F-FCholine: 0.08 (0.02 to 0.44) **^{64}Cu-PSMA-617** vs ^{18}F-FCholine: 0.59 (0.21 to 1.64) **^{68}G-PSMA-11** vs ^{11}C-Choline: 0.81 (0.40 to 1.62) **^{68}G-PSMA-11** vs **^{18}F-DCFPyL**: 1.00 (0.35 to 2.87) **^{68}G-PSMA-11** vs ^{18}F-FACBC: 0.73 (0.36 to 1.50) **^{68}G-PSMA-11** vs ^{18}F-FCholine: 0.81 (0.38 to 2.60) **Overall positivity RR (95%CI) - Network meta-analysis (RR < 1 favours 1st tracer)** **^{18}F-PSMA-1007** vs ^{11}C-Choline: 0.52 (0.17 to 1.55) **^{18}F-PSMA-1007** vs **^{18}F-DCFPyL**: 0.64 (0.16 to 2.49) **^{18}F-PSMA-1007** vs ^{18}F-FACBC: 0.47 (0.15 to 1.43) **^{18}F-PSMA-1007** vs ^{18}F-FCholine: 0.33 (0.11 to 0.94)* **^{18}F-PSMA-1007** vs **^{64}Cu-PSMA-617**: 1.82 (0.42 to 7.90) **^{18}F-PSMA-1007** vs **^{68}G-PSMA-11**: 1.56 (0.66 to 3.68) **^{64}Cu-PSMA-617** vs ^{11}C-Choline: 0.94 (0.21 to 4.25) **^{64}Cu-PSMA-617** vs **^{18}F-DCFPyL**: 1.17 (0.21 to 6.41) **^{64}Cu-PSMA-617** vs ^{18}F-FACBC: 0.85 (0.19 to 3.89) **^{64}Cu-PSMA-617** vs ^{18}F-FCholine: 0.59 (0.21 to 1.22) **^{64}Cu-PSMA-617** vs **^{68}G-PSMA-11**: 0.86 (0.22 to 3.27) **^{68}G-PSMA-11** vs ^{11}C-Choline: 0.81 (0.40 to 1.62) **^{68}G-PSMA-11** vs **^{18}F-DCFPyL**: 1.00 (0.35 to 2.87) **^{68}G-PSMA-11** vs ^{18}F-FACBC: 0.73 (0.36 to 1.50) **^{68}G-PSMA-11** vs ^{18}F-FCholine: 0.51 (0.21 to 1.22) **^{18}F-DCFPyL** vs ^{11}C-Choline: 0.81 (0.23 to 2.85) ^{18}F-FACBC vs **^{18}F-DCFPyL**: 1.37 (0.38 to 4.91) ^{18}F-FCholine vs **^{18}F-DCFPyL**: 1.96 (0.50 to 7.71) * *P* < 0.05, PSMA based tracers indicted in bold							"Current evidence suggests that PSMA PET/CT for prostate cancer restaging in patients with BCR achieves best detection rates (over 70%) if PSA is >1 ng/ml. At lower PSA levels, the detection rate of PSMA PET/CT is lower (33.7% for PSA <0.2 ng/ml and 50% for PSA 0.2-0.49 ng/ml), despite being better than "older" tracers such as Choline-based PET or CT/bone scintigraphy. Furthermore, no PSMA tracer can be currently considered superior to others. Further studies are needed to better define the diagnostic performance and role of these imaging techniques." (page 12)
Evangelista et al., (2020)[6]							
Most summaries of the included studies combined different radiotracers for PET/MRI imaging of prostate cancer. **MA of DR (95% CI) for restaging** All reports: 0.809 (0.730 to 0.869) PSMA PET/MRI: 0.818 (0.724 to 0.884) Choline PET/MRI: 0.773 (0.537 to 0.909)							"PET/MRI proved highly sensitive in detecting primary PCa, with a high detection rate for recurrent disease, particularly when radiolabeled PSMA was used." (page 1) "However, no comparative data are now available about radiolabeled PSMA and radiolabeled choline PET/MRI in the same population, in each phase of disease (i.e., staging or restaging)." (page 9) "The heterogeneity between the studies was high (> 80%). There

Main study findings		Authors' conclusion
		was also evidence of publication bias, as illustrated by the funnel plot" (page 10)
Kimura et al., (2020)[7]		
Lesion-based analysis PET/CT ^{68}G-PSMA-11 (MA of 5 studies)		"PSMA-PET before sLND provided highly accurate performance with clinically relevant high positive and negative predictive values for detecting lymph node disease in patients with BCR after local treatment with curative intent for PCa." (page 1). "Larger, well-designed prospective studies are necessary to validate these findings and expand the diagnostic and therapeutic indications for the PSMA-PET in PCa." (page 9)
Sensitivity	0.84 (0.61 to 0.95)	
Specificity	0.97 (0.95 to 0.99)	
LR+	30.3 (14.5 to 63.4)	
LR-	0.16 (0.06 to 0.46)	
DOR	189 (39 to 920)	
Field-based analysis PET/CT ^{68}G-PSMA-11 (MA of 4 studies)		
Sensitivity	0.82 (0.72 to 0.89)	
Specificity	0.95 (0.70 to 0.99)	
LR+	15.8 (2.1 to 116.6)	
LR-	0.16 (0.06 to 0.46)	
DOR	82 (8 to 832)	
Perera et al., (2020)[9]		
PET/MRI ^{68}G-PSMA-11 (MA of 5 studies with pathologic correlation)		"The importance of early and accurate detection of low volume metastases in advanced prostate cancer has prompted the introduction of ^{68}Ga-PSMA-11 PET. Following pooled analysis, the results of the current study suggest that pre-PET PSA predicts the risk of metastatic disease diagnosed by ^{68}Ga-PSMA-11 PET. This novel imaging modality appears to provide superior sensitivity and specificity values compared with alternate techniques." (page 415)
	Se (95% CI) / **Sp (95% CI)**	
Per Patient	0.77 (0.46 to 0.93) / 0.97 (0.91 to 0.99)	
Per Lymph node	0.75 (0.58 to 0.87) / 0.99 (0.97 to 1.00)	
Tan et al., (2020)[17]		
Detection Rate of Posttreatment Patient with PSA < 0.5 ng/mL (95% CI)		"In conclusion, these results demonstrate a significantly higher detection rate of gallium 68 or fluorine 18 (18F) prostate-specific membrane antigen PET/CT over 18F-Fluciclovine PET/CT when the prostate-specific antigen (PSA) level is 1.0–1.9 ng/mL." "Future analyses should consider the impact of publication bias and heterogeneity on results interpretation." (page 53)
^{68}G or ^{18}F-PSMA (33 studies)	45.2% (37.9 to 52.5)	
^{18}F-fluciclovine (2 studies)	36.9% (25.0 to 48.8)	
Difference	8% (-22 to 38) (*P* = 0.46)	
Detection Rate of Posttreatment Patient with PSA 0.5 to 0.9 ng/mL (95% CI)		
^{68}G or ^{18}F-PSMA (29 studies)	58.7% (51.7 to 65.8)	
^{18}F-fluciclovine (6 studies)	47.6% (34.5 to 60.7)	
Difference	11% (-6 to 28) (*P* = 0.19)	
Detection Rate of Posttreatment Patient with PSA 1.0 to 1.9 ng/mL (95% CI)*		
^{68}G or ^{18}F-PSMA (33 studies)	79.9% (74.6 to 85.3)	
^{18}F-fluciclovine (2 studies)	62.1% (54.5 to 69.6)	
Difference	18% (5 to 30) (*P* = 0.01)	

Main study findings	Authors' conclusion
*$P < 0.05$	
Turpin et al., (2020)[12]	
Imaging method for LN staging (study) / **Se** / **Sp** PSMA PET/CT (Primary, 130 patients) 0.659 0.989 PSMA PET/CT (MA, 298 patients) 0.71 0.95 CT scan (Review, 4262 patients) 0.07 1.0 CT scan (MA, 1024 patients) 0.42 0.82 Choline-PET/CT (MA, 177 patients) 0.91-1.0 0.66-0.997 MRI (MA, 177 patients) 0.188-0.697 0.786-0.976 MRI (MA, 628 patients) 0.39 0.82 MRI w/ magnetic nanoparticles (Primary, 33 patients) 0.905 0.978 **Imaging method for SVI (study)** / **Se** / **Sp** PSMA PET/CT (Primary, 21 patients) 0.73 1.0 MRI (Primary, 527 patients) 0.759 0.947 Choline PET/CT (Primary, 47 patients) 0.36 0.98 **Imaging method for biological relapse (123 patients)** DR(%) / LR(%) / BR(%) / LNR(%)* PSMA PET/CT 83 - 98 94 Choline PET/CT 79 - 64 71 *($P < 0.05$) **Imaging method for biological relapse (50 patients)** DR(%) / LR(%) / BR(%) / LNR(%) PSMA PET/CT 56 14 8 30 ^{18}F-FCholine PET/CT 26 18 0 8 **Imaging method for biological relapse in bone metastasis (60 patients)** **Se** / **Sp** PSMA PET/CT 0.80 1.0 NaF PET 0.90 0.98 MRI 0.25 0.87	"Prospective data also shows clear superiority of PSMA PET or ^{18}F-Fluciclovine-PET to Choline-PET.""However, whether one of these radiotracers improves patient survival over the other is unknown and further research is needed to determine which has the greater effect." (page 11) "Albisinni et al. studied the clinical impact of PSMA PET in patient management and found a change in the treatment plan for 76% of patients (85). This new imaging modality is very promising and might be at the center of treatment planning in the BCR setting in the future, especially for oligometastatic patients." (page 9)
Wang et al., (2020)[20]	
Meta-analysis of 6 ^{68}G-PSMA-11 PET/MRI studies with pathologic correlation **Se (95% CI)** / **Sp (95% CI)** Per lesion 0.83 (0.73 to 0.90) 0.81 (0.61 to 0.92) **Meta-analysis of 7 ^{68}G-PSMA-11 PET/MRI studies with pathologic correlation** **DR (95%CI)** Any PSA level (7 studies) 76% (72 to 79) PSA < 0.19 ng/mL (1 studies) 38% (20 to 57) PSA 0.2 to 0.99 ng/mL (4 studies) 67% (57 to 78) PSA 1 to 1.99 ng/mL (3 studies) 74% (56 to 92) PSA > 2 ng/mL (3 studies) 95% (90 to 1.00)	"… the diagnostic accuracy of ^{68}Ga-PSMA-11 PET/MRI in patients with BCR was also high, positively correlating with PSA levels." (page 1)
De Visschere et al., (2019)[5]	
PSMA PET/CT "In patients with recurrent PCa, higher detection rates than any other imaging modality are observed, especially for smaller lesions at low PSA values." "In our systematic review, eight papers report the detection rates of 68Ga PSMA-11 PET-CT at PSA levels <0.2	"The role of imaging in the setting of early recurrent PCa is to demonstrate the localization of the relapse, which may be local in the

Main study findings	Authors' conclusion
ng/ml. The detection rates ranged from 11.3% to as high as 58.3%. In patients with PSA <0.5 ng/ml, detection rates ranged from 11.0% to 65.0%. In a study of Afshar-Oromieh et al., lesion-based sensitivity of 76.6%, specificity of 100%, NPV of 91.4%, and PPV of 100% were reported. Thus, ^{68}Ga PSMA-11 PET-CT has very high specificity but moderate sensitivity for lymph node metastasis detection, which may imply some underestimation of disease load (although less pronounced than with other PET tracers). Other disadvantages of ^{68}Ga PSMA- 11 are urinary excretion and some tumors that appear to have no or only very low expression of PSMA. Despite these limitations, ^{68}Ga PSMA-11 PET-CT appears to allow for more complete and accurate restaging of PCa patients compared with standard routine imaging. Nowadays, ^{68}Ga PSMA-11 PET-CT is increasingly being performed worldwide, but in many countries it is not available." (page 67) **^{68}G-PSMA-11** "Higher detection rates than any other imaging modality especially in the range of low PSA values (< 0.5 ng/mL)" (page 63) **^{18}F-DCFPyL** "Noninferior to ^{68}G-PSMA-11 while offering the advantages of ^{18}F-labeling." (page 63). **^{18}F-DCFBC** "^{18}F-labeled PSMA-targeted tracer but limited evidence in the early recurrence setting" (page 63)	treated prostatic area, lymph nodes, or distant metastasis. The detection rates depend on the level of the PSA at the time of imaging. CT and BS are traditionally used, but they are not sufficiently sensitive to localize recurrence at low PSA values. Multiparametric MRI is a valuable imaging modality for the detection of local recurrence and is often combined with PET-CT for the assessment of distant disease. Newer techniques such as wbMRI, PET-MRI, or PETCT, especially with PSMA-directed tracers, allow for an all-in-one approach, even at very low recurrent PSA values. Imaging should be performed only if the outcome influences subsequent treatment decisions." (page 71)
Hope et al., (2019)[10]	
Meta-analysis of 15 ^{68}G-PSMA-11 studies of biochemical recurrence with pathologic correlation (256 patients) Se (95% CI) 0.99 (0.96 to 1.0) Sp (95% CI) 0.76 (0.01 to 1.0) PPV (95% CI) 0.99 (0.96 to 1.0) NPV (95% CI) 0.76 (0.02 to 1.0) "Given that only PSMA-positive lesions were biopsied and the resultant low number of true- and false- negative lesions, the most relevant measurement in this population is the PPV" (page 787)	"68Ga-PSMA-11 performed well for the localization of metastatic prostate cancer. In biochemical recurrence, with pathology as a gold standard, the PPV was 0.99 (95% CI, 0.96–1.00)." (page 791)
Moghul et al., (2019)[11]	
Detection rate (OR (95% CI), OR > 1 favours ^{68}G-PSMA-11 PET/CT ^{68}G-PSMA-11 vs radiolabeled choline PET/CT (overall) 2.27 (1.06 to 4.85)* ^{68}G-PSMA-11 vs radiolabeled choline PET/CT (PSA < 2 ng/mL) 2.37 (0.61 to 9.17) "There were no reports of any adverse effects in any of the publications." (page 5)	"PSMA PET/CT scans have a better performance compared with radiolabeled choline PET/CT scans in detecting recurrent disease following initial curative treatment for prostate cancer, both on a per-patient and per-lesion analysis. PSMA PET/CT scans should be the imaging modality of choice while deciding on salvage and nonsystematic metastasis-directed therapy strategies." (page 8)
Sathianathen et al., (2019)[8]	
PET/CT Tracer/patient **Se (95% CI)** **Sp (95% CI)** ^{11}C-Choline (16 studies) 0.809 (0.704 to 0.883) 0.841 (0.702 to 0.922) ^{18}F-FACBC (4 studies) 0.797 (0.519 to 0.934) 0.619 (0.411 to 0.790)	"There is a lack of high-quality data to verify the accuracy of PET-based imaging using 11C-Choline,

Main study findings				Authors' conclusion
PET/CT Tracer/lesion	**Se (95% CI)**	**Sp (95% CI)**		18F-FACBC, or 68Ga-PSMA. The early results are encouraging that these techniques are superior to conventional imaging modalities, which would allow salvage therapies to be optimized." (page 1239)
^{18}F-FACBC (1 study)	0.627 (0.564 to 0.685)	0.698 (0.645 to 0.747)		
^{68}Ga-PSMA-11 (1 study)	0.764 (0.683 to 0.829)	0.998 (0.975 to 1.00)		
PET/CT Tracer/patient	**LR+**	**LR-**	**DOR**	
^{11}C-Choline (16 studies)	5.4	0.24	25.2	
^{18}F-FACBC (4 studies)	2.1	0.36	8.0	
Tan et al., (2019)[16]				
Pooled Detection Rate/Patient of BCR Patient (95% CI) using PSMA PET/CT				"PSMA targeted radiotracers are likely effective for detecting biochemically recurrent prostate cancer at low PSA levels." "However, existing studies are heterogeneous and limited by retrospective design, publication bias and limited reference standards." (page 238)
Any PSA level (43 studies)	70.2% (65.0 to 75.4)			
PSA < 0.5 ng/mL (24 studies)	44.9% (36.0 to 53.9)			
PSA 0.5 to 0.9 ng/mL (19 studies)	61.3% (52.3 to 70.3)			
PSA 1 to 1.9 ng/mL (15 studies)	78.2% (70.8 to 85.6)			
PSA > 2 ng/mL (20 studies)	93.9% (92.0 to 95.8)			
Treglia et al., (2019)[18]				
Pooled Detection Rate/Patient of BCR Patient (95% CI) using ^{18}F-PSMA PET/CT				"18F-labeled PSMA PET/CT demonstrated a good DR in BRPCa, in particular using 18F-PSMA-1007 and 18F-DCFPyL, with similar results compared to those reported in the literature with 68Ga-labeled PSMA PET/CT. The DR of 18F-labeled PSMA PET/CT is related to PSA values with significant lower DR in patients with PSA < 0.5 ng/mL." (page 12)
Any PSA level (6 studies)	81% (71 to 88)			
PSA ≥ 0.5 ng/mL (5 studies)	86% (78 to 93)			
PSA < 0.5 ng/mL (5 studies)	49% (23 to 74)			
PSA 0.5 to 0.9 ng/mL (4 studies)	73% (59 to 85)			
PSA 1 to 1.9 ng/mL (4 studies)	88% (73 to 97)			
PSA > 2 ng/mL (4 studies)	92% (83 to 98)			
Treglia et al., (2019)[19]				
Meta-analysis of Detection Rate/Patient of BCR Patient (95% CI) (MA of 5 studies)	**Choline PET/CT**	**PSMA PET/CT**		"Radiolabelled PSMA PET/CT proved to be clearly superior in detecting BRPCa lesions at low PSA levels (≤ 1 ng/ml) when compared to radiolabelled radiolabeled choline PET/CT. On the other hand, the superiority of radiolabelled PSMA PET/CT was less evident and not statistically significant in patients with higher PSA levels. More studies comparing these imaging methods and cost-effectiveness analyses are warranted." (page 135)
Any PSA level	56% (37 to 75)	78% (70 to 84)		
PSA ≤ 1 ng/mL	27% (17 to 39)	54% (43 to 65)*		
PSA > 1 ng/mL	72% (59 to 84)	88% (83 to 92)		

Main study findings	Authors' conclusion
Zhou et al., (2019)[21]	
Diagnostic Accuracy/Patient of Bone Metastases (95% CI) (MA of 23 studies) **Se** / **Sp** ^{68}Ga-PSMA-11 PET/CT: 0.97 (0.89 to 0.99) / 1.00 (0.00 to 1.00) Radiolabeled choline PET/CT: 0.87 (0.80 to 0.92) / 0.99 (0.96 to 1.00) ^{18}F-NaF PET/CT: 0.96 (0.87 to 0.99) / 0.97 (0.90 to 0.99) MRI: 0.91 (0.87 to 0.99) / 0.96 (0.92 to 0.98) BS: 0.86 (0.76 to 0.92) / 0.95 (0.87 to 0.92) **Diagnostic Accuracy/Lesion of Bone Metastases (95% CI) (MA of 23 studies)** **Se** ^{68}Ga-PSMA-11 PET/CT: 0.88 Radiolabeled choline PET/CT: 0.80 ^{18}F-NaF PET/CT: 0.97 MRI: 0.81 BS: 0.68	"Our meta-analysis showed that PSMA-PET/CT and ^{18}F-NaF PET/ CT had higher diagnostic value for bone metastasis of prostate cancer than Choline-PET/CT, MRI, and BS. BS is widely used in hospitals, so it may be the best choice in routine examination of prostate cancer. PSMA PET/CT and ^{18}F-NaF PET/ CT can be selected for further examination if needed." (page 1922)

CI = confidence interval; BCR = biochemical recurrence; BR = bone recurrence; BRPCa = biochemically recurrent prostate cancer; CT = computed tomography; DOR = diagnostic odds ratio; DR = disease detection rate; MA = meta-analysis; LNR = lymph node recurrence; LR = local recurrence; LR+ = positive likelihood ratio; LR- = negative likelihood ratio; MRI = magnetic resonance imaging; OR = odds ratio; PET/CT = positron emission tomography/computed tomography; PET/MRI = positron emission tomography/magnetic resonance imaging; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen; RR = risk ratio; Se = sensitivity; Sp = specificity; SVI = seminal vesicle invasion

Table 10: Summary of Recommendations in Included Guideline

Recommendations and supporting evidence	Quality of evidence and strength of recommendations
AUA/ASTRO/SUO Guidelines, 2020[22,23]	
For Patients with BCR without metastatic disease after exhaustion of local treatment options: Clinicians may utilize novel PET-CT scans (e.g., ^{18}F-Fluciclovine, Choline, PSMA) in patients with PSA recurrence after failure of local therapy as an alternative to conventional imaging or in the setting of negative conventional imaging. (**Expert Opinion**)	The only recommendation that is specific to PSMA PET/CT is rated as "**Expert Opinion**" which is a statement, achieved by consensus of the Panel, that is based on members' clinical training, experience, knowledge, and judgement for which there may or may not be evidence in the medical literature. The evidence supporting such recommendations do not include a strength of evidence category. These guidelines also state that only ^{11}C-Choline and ^{18}F-FCholine are FDA approved for PET imaging for staging of patients with BCR of PCa.

BCR = biochemical recurrence; FDA = Food and Drug Administration; PCa = prostate cancer; PET/CT = positron emission tomography/computed tomography; PSA = prostate-specific antigen; PSMA = prostate-specific membrane antigen

Appendix 5: Overlap between Included Systematic Reviews

Table 11: Overlap in Relevant Primary Studies between Included Systematic Reviews