

CADTH ENVIRONMENTAL SCAN

Pharmaceuticals Requiring Companion Diagnostics

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Background and Context

The purpose of this Environmental Scan is to provide an overview of the current and projected use of companion diagnostic tests required for the prescription of targeted drug therapies, as well as the regulatory and reimbursement processes for these devices and drugs both nationally and internationally. The information is intended to inform policy- and decision-makers in understanding this unique area of medicine. It also highlights the potential financial implications associated with the introduction of companion diagnostics for the future.

In the past two decades, with the increasing understanding of molecular drivers of disease, discovery of many biomarkers, and the subsequent development of targeted pharmaceutical treatments, the development and use of companion diagnostics has significantly increased. There are various terminologies in use to describe the clinical application of these technologies, such as personalized medicine, targeted medicine, and precision medicine. The common link to the different terminologies is that a diagnostic test is used to select patients who are most likely to benefit from a particular intervention (which could lead to either ruling in or ruling out treatment, depending on the intervention and medical condition). Different definitions have been proposed for personalized medicine, including, but not limited to, the following:

- In the US, the Personalized Medicine Coalition defines personalized medicine as the “tailoring of medical treatment to the individual characteristics of each patient. It does not mean that drugs (or medical devices) are developed to be unique to a patient but rather the ability to classify individuals into subpopulations that differ in their susceptibility to a particular disease or their response to a specific treatment. Preventive or therapeutic interventions can then be concentrated on those who will benefit, sparing expense and adverse effects for those who will not.”¹
- The US National Cancer Institute refers to personalized medicine as “a form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease.”²
- In Canada, the Personalized Medicine Working Group (PMWG), a working group established in 2009 by Health Canada, refers to personalized medicine as “the tailoring of medical interventions to individual characteristics of each patient.”³

The concept of personalized medicine has stemmed from the advancement of technology, including diagnostic tests that help to guide the choice of therapy based on individual characteristics. Although the potential benefits of personalized medicine are substantial, from increased therapeutic efficacy and safety of pharmaceuticals to lower medical costs, the uptake by health systems remains limited at this time.⁴ However, it is anticipated that, as scientific understanding of disease at the molecular level becomes more prevalent, personalized medicine approaches to diagnosis and treatment will become more common. For example, the number of personalized medicine technologies commercialized in Europe quadrupled between 2006 and 2011.¹ In addition, in the US, development of therapeutic products that are paired with diagnostic tests is becoming more common.⁵ In December 2013, the FDA approved the first genomic sequencer for commercial use in the US. The approval of this platform makes possible the generation of genomic information in clinical practice and will likely expand the use of this information to guide patient care.⁶ Some of the key features of personalized medicine include:⁵

- identifying populations that are candidates for treatment including subpopulations that may be most likely to derive increased benefit from treatment
- identifying populations that should not receive treatment because of increased risk of serious adverse effects.

As previously indicated, Health Canada established the PMWG in December 2009, acknowledging the need for a “concerted portfolio policy approach to personalized medicine.”³ The mandate of this working group was to conduct a comprehensive policy analysis on personalized medicine. This mandate was based on the need to ensure that there is a coordinated approach that protects and promotes the health of Canadians, while maximizing the advantages offered by personalized medicine. Some of the related activities in which Health Canada was involved include the development of a pharmacogenomics guidance document, regulatory modernization, and participation in the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) E15 and E16 initiatives.⁷ These two initiatives produced guidelines respectively aimed at defining terminology and data related to pharmacogenomics and pharmacogenetics,⁸ as well as guiding regulatory submissions for the qualification of genomic biomarkers.⁹ The ICH E15 and E16 initiatives stemmed from the ICH — a unique organization bringing together the regulatory authorities and pharmaceutical industry of Europe, Japan, and the US to discuss scientific and technical aspects of drug registration.¹⁰ Of interest, ICH defines pharmacogenomics as “the study of variations of DNA and RNA characteristics as related to drug response,” and pharmacogenetics as “the study of variations in DNA sequence as related to drug response.”⁸ These definitions appear in a recent Health Canada guidance document *Adoption of ICH1 guidance: Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories — ICH Topic E15*.¹¹ This document also defines a genomic biomarker as a measurable DNA and/or RNA characteristic that is an indicator of a normal biologic process, pathogenic processes, and/or a response to therapeutic or other interventions.¹¹

Companion diagnostic tests are used to measure an individual’s protein or gene expression, or detect genetic variation (biomarkers).¹² The detection or concentration of certain biomarkers may then influence the choice of drug therapy, as several drugs are known to be effective only in specific subgroups of patients with a particular disease. The FDA defines such diagnostic tests as in vitro diagnostic (IVD) companion diagnostic devices; i.e., IVD devices that provide information that is essential for the safe and effective use of a corresponding therapeutic product.⁵ An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

- “Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of the treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
- Identify patients in the population for whom the therapeutic product has been adequately studied and found safe and effective; i.e., there is insufficient

information about the safety and effectiveness of the therapeutic product in any other population.”⁵

The FDA does not include in this definition IVD tests that are not essential to the safe and effective use of a therapeutic product; e.g., commonly used clinical laboratory tests such as serum creatinine or transaminases.⁵

In the United Kingdom (UK), the National Institute for Health and Care Excellence (NICE) defines companion diagnostic tests as diagnostic technology that identifies people who are likely to benefit from specific therapies for their conditions. These tests may also help in stratifying disease status, selecting the proper medication, and tailoring dosages to patients’ needs. In some cases, the use of companion diagnostic technologies may be necessary to comply with the licensed indications of pharmaceuticals.¹³ It should be noted that other pharmacogenomics tests may also be used to guide therapy and that such tests may not always strictly meet the definition of companion diagnostics. A recent example is a test that guides therapy with simeprevir, an antiviral drug used to treat chronic hepatitis C virus (HCV) infection. Simeprevir is less effective in patients infected with HCV genotype 1a containing the NS3 Q80K polymorphism. Screening patients for the presence of the virus with the NS3 Q80K polymorphism is therefore recommended.¹⁴ Of note, in such cases it is not the patient who is being tested but the virus. In this case, the test is intended to detect whether the virus is resistant to the antiviral drug, not to determine whether a genetic mutation is carried by the patient and could influence his or her response to the drug.

As previously stated, the use of genetic variation (biomarkers) to determine individual responses to drug therapy is also known as pharmacogenomics. In that context, companion diagnostics can be used to guide the choice and/or dose of a particular drug therapy and improve patient outcomes. This approach also has the potential for reducing treatment costs.^{15,16}

Many companion diagnostic tests are recommended prior to prescribing a specific drug therapy; however, a subset of companion diagnostics are required (i.e., testing of biomarkers prior to prescribing the companion drug). Required companion diagnostics are typically developed alongside the targeted therapy, where the biomarker can be identified, verified, and utilized in the same clinical trials. In these cases, the required companion diagnostic can be submitted for regulatory approval with the associated therapy, usually as a combination product. Examples of therapeutic products that have been co-approved in the US with their companion diagnostics include Herceptin (trastuzumab), Zelboraf (vemurafenib), Xalkori (crizotinib), Erbitux (cetuximab), Kadcylla (ado-trastuzumab emtansine), Tafinlar (dabrafenib), Mekinist (trametinib), Tarceva (erlotinib), Giotrif/Gilotrif (afatinib), Perjeta (pertuzumab), Vectibix (panitumumab), and Lynparza (olaparib).¹⁷⁻¹⁹ Alternatively, companion diagnostic tests that are required for prescribing may be developed and approved after the associated therapy has received market approval or when a new indication for the approved therapy may require a different companion diagnostic test to identify a new biomarker. In these cases, the regulatory labelling on the pharmaceutical is changed from “recommended” to “required.”¹⁸ Of note, the actual wording used in the drug product label to describe the companion testing requirements may vary depending on the country where the pharmaceutical and the diagnostic test are approved.

As previously stated, the FDA makes a distinction in the drug label between diagnostic tests that are listed as “required” to determine the appropriate patient and drug

selection versus those that are listed in the drug label as “recommended” or “available”. Only the tests that are “required” are formally recognized as “companion diagnostics”^{5,20} and will be the focus of this Environmental Scan. Also, for the purpose of this Environmental Scan, the term “pharmaceuticals” refers to both drugs and biologics.

Objectives

The key objectives of this Environmental Scan are to address the following questions:

- What is the current landscape of pharmaceuticals that require a companion diagnostic to identify patients who are likely to benefit the most from therapy?
- What is the expected magnitude of pharmaceuticals that will require a companion diagnostic across all therapeutic areas over the next five to 10 years?
- How is the companion diagnostics environment evolving with regard to co-development and collaboration between the pharmaceutical industry and device manufacturers?
- What are the current and emerging regulatory practices for:
 - pharmaceuticals that require a companion diagnostic
 - diagnostic tests required for the optimal use of a pharmaceutical?
- What are the current and emerging reimbursement practices for:
 - pharmaceuticals that require a companion diagnostic
 - diagnostic tests required for the optimal use of a pharmaceutical?
- What is the potential financial impact of such technologies, particularly on the public payers?

Findings

The findings of this Environmental Scan are not intended to provide a comprehensive review of the topic. Results are based on a focused literature search; a draft version of the report was also posted and feedback solicited from 103 different stakeholders in the summer of 2014; responses were received from two pharmaceutical companies and three professional associations. This report is based on information gathered as at August 2014; a partial update (mainly of landscape, pipeline, and regulatory information) was conducted in 2015.

Current Landscape of Pharmaceuticals That Require a Companion Diagnostic

Currently available companion diagnostic tests aim to detect a single biomarker or genetic variance in a single gene; in the future, whole genome sequencing and genomic profiling of tumours or individuals may be possible.²¹

Companion diagnostics is a rapidly growing area, as demonstrated by the growing number of available companion diagnostic tests on the market.¹⁹ The majority of companion diagnostics are being developed for oncology.^{19,22,23} However, companion diagnostics development is a growing area for other therapeutic areas as well, including neurology, cardiology, gastrointestinal and musculoskeletal disorders.²³ Examples of other approved indications with companion diagnostic tests include cystic fibrosis, human immunodeficiency virus, and severe growth failure.¹⁹

Examples of pharmaceuticals approved in Canada and the associated biomarker targets required for the companion diagnostic tests can be found in Table 1. A more detailed list of approved therapies with an associated companion diagnostic test can be found in Appendix 1, Table 10.

Table 1: Examples of Therapies and Associated Biomarkers²⁴

Therapy ^a	Indication	Biomarker	Target
Trastuzumab	Oncology	<i>ERBB2</i>	HER2 protein over-expression positive
Vemurafenib	Oncology	<i>BRAF</i>	<i>BRAF</i> V600E mutation-positive
Dabrafenib	Oncology	<i>BRAF</i>	<i>BRAF</i> V600E/K mutation-positive
Trametinib	Oncology	<i>BRAF</i>	<i>BRAF</i> V600E/K mutation-positive
Cetuximab	Oncology	<i>KRAS</i>	<i>KRAS</i> codon 12 and 13 mutation- negative
Crizotinib	Oncology	<i>ALK</i>	<i>ALK</i> gene rearrangement-positive
Erlotinib	Oncology	<i>EGFR</i>	<i>EGFR</i> mutation
Afatinib	Oncology	<i>EGFR</i>	<i>EGFR</i> exon 19 deletion or exon 21 substitution (L858R)-positive

ALK = anaplastic lymphoma receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *EGFR* = epidermal growth factor receptor; *ERBB2* = erb-b2 receptor tyrosine kinase 2; *HER2* = human epidermal growth factor receptor 2; *KRAS* = Kirsten rat sarcoma viral oncogene homolog.

^a All of the therapies listed in the table are approved for use in Canada and the United States.

Examples of approved companion diagnostic tests available in Canada — the use of which is required to guide the associated drug therapy — can be found in Table 2. A more detailed list of approved companion diagnostic tests can be found in Appendix 2, Table 11.

Table 2: Examples of Approved Companion Diagnostic Tests in Canada²⁵

Diagnostic Test	Therapy	Identification by CDx
Cobas 4800 BRAF V600 Mutation Test	Vemurafenib	V600E mutation in the <i>BRAF</i> gene
HercepTest Kit	Trastuzumab	Tumour over-expression of <i>HER2</i>

BRAF = B-Raf proto-oncogene, serine/threonine kinase; CDx = companion diagnostic; *HER2* = human epidermal growth factor receptor 2.

As of the end of 2015, the pan-Canadian Oncology Drug Review (pCODR) had completed 13 reviews of targeted therapies for cancer treatment; these required five different companion diagnostic tests (Table 3).²⁵

Table 3: pCODR Completed Reviews of Targeted Therapies With Companion Diagnostics²⁵

Drug	Biomarker
Vemurafenib	<i>BRAF</i> V600
Crizotinib	<i>ALK</i>
Pertuzumab	<i>HER2/neu</i>
Lapatinib	<i>HER2/neu</i>
Trastuzumab emtansine	<i>HER2/neu</i>
Dabrafenib	<i>BRAF</i> V600
Trametinib	<i>BRAF</i> V600
Cetuximab	<i>KRAS</i>
Afatinib	<i>EGFR</i>
Peruzumab	<i>HER2</i>
Dabrafenib + Trametinib combination	<i>BRAF</i> V600
Panitumumab	<i>KRAS</i>
Ceritinib	<i>ALK</i>

ALK = anaplastic lymphoma receptor tyrosine kinase; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; *HER2* = human epidermal growth factor receptor 2; *KRAS* = Kirsten rat sarcoma viral oncogene homolog.

Expected Magnitude of Required Companion Diagnostic Tests During the Next Five to 10 Years

In 1998, the first companion diagnostic (HercepTest, Dako) was approved, alongside the companion drug (Herceptin).²⁶ Indeed, both the drug product (Herceptin, Genentech USA, Inc.) and the companion test kit (HercepTest, Dako) received regulatory approval from the FDA on the same day: September 25, 1998. This synchronized timing likely resulted from the collaboration between Genentech and Dako, which had started several months earlier.²⁷ Subsequently, many more companion diagnostics have been approved either with co-developed drugs or added to therapies already on the market.^{17,28,29}

A recent article in *Forbes* notes that the market for companion diagnostic test sales and test services alone was US\$2.4 billion in 2014, and this number is expected to reach US\$6.9 billion globally.²³ By 2020, the companion diagnostics market is expected to experience a growth of 20.4% globally.²³

As a reflection of the increased attention given by the health care industry toward personalized medicine and targeted pharmacological therapies with companion diagnostics, several health market research companies now conduct evaluations and surveys in this domain. Advertisements for reports published by these companies provide an idea of the market trends and confirm the expected importance of this form of treatment in the future. Examples follow.

- The global market for companion diagnostics is expected to significantly grow in the future, with compound annual growth rate (CAGR) varying between 18.1% and 23.9%. Of note, potential differences in the definition used for market values may explain differences reported, as follows:
 - One market research company reports that the value of the global market for companion diagnostics is projected to increase from US\$1.8 billion (in 2013) to US\$5.6 billion by 2019; this represents a projected CAGR of 18.1% for the forecast period.³⁰
 - Another market research company indicates that the global companion diagnostics market reached US\$1.1 billion in 2012 and US\$1.2 billion in 2013, respectively, and will progress to US\$3.5 billion in 2018. This represents a projected CAGR of 23.9% for the period.³¹
 - A third company projects that the global market value of companion diagnostics is expected to grow from US\$3.1 billion in 2014 to US\$8.7 billion in 2019, representing an anticipated CAGR of 22.7% for the forecast period.³²
- The global market composed of targeted pharmacological therapies and companion diagnostics is projected to grow from a current value of US\$42 billion to more than US\$60 billion by 2019.^{33,34} This projection represents a calculated growth rate of at least 43 % over the next four years. It may therefore be estimated that the CAGR would be approximately 9.3%. Key segments of this market include oncology, cardiovascular disease, as well as infectious diseases treatment and diagnostics.^{33,34}
- A number of factors will contribute to the growth of the global companion diagnostics market including, among others, supportive government initiatives, a growing need for targeted cancer treatment, increasing disposable income, technological advancement, rise in cost of drug discovery, increasing the adoption of companion diagnostics by reference laboratories and pharmaceutical companies, as well as increasing the awareness about personalized health care and increasing demand for better health care facilities.³⁵
- Other factors may restrain the development of the companion diagnostics market including, among others, reimbursement issues, the availability of non-validated laboratory-developed (home-grown) tests, regulatory restrictions, and the time required for approval, as well as high cost.³⁵
- It appears that the global companion diagnostics market is currently dominated by a limited number of companies. Recent advertisement from a market research company reported that five companies (Roche Diagnostics in Switzerland, Abbott Laboratories in the US, Agilent Technologies in the US, QIAGEN in Germany, and Thermo Fisher Scientific Inc. in the US) together occupied up to 86% of this market in 2013.³²

The future growth of companion diagnostics is partially based on the potential for the co-development and approval of new therapies requiring a companion diagnostic on their label. In Roche's 2014 annual report, it was highlighted that Roche offers six medicines requiring a companion diagnostic test, and that 50% of their products in development were being developed within personalized health care.³⁶

Table 4 provides examples of anticipated therapies based on information from websites of companies that are manufacturers of therapies with companion diagnostics.

Table 4: Pipeline Pharmaceuticals Requiring Companion Diagnostic^a

Company	Pharmaceuticals	Indication	Phase of Approval or Development	Diagnostic Company	CDx Test	Source
Merck	MK-8931 BACE	Alzheimer disease	Phase III	Luminex	Luminex's xMAP Technology to measure concentrations of Aβ42 and t-tau in CSF	Merck & Co., Inc., 2013 ^{37,38}
Merck	MK-3475/ lambrolizumab/ pembrolizumab (antibody designed to target the PD-1)	Melanoma and NSCLC	Phase I and II	Dako	PD-L1 (potential tumour biomarker)	Merck Canada Inc., Kirkland, QC: personal communication, July 2014
Janssen Pharmaceutica NV	Unknown	Heart failure	Unknown	Siemens Healthcare Diagnostics	NA	IVD Technology 2013 ³⁹
Novartis	Nilotinib	Chronic myeloid leukemia	Unknown	NA	<i>BCR/ABL</i> (Version 2)	Novartis Oncology 2012 ⁴⁰
Novartis	BKM120 BEZ235 BYL719	Breast, NSCLC, prostate cancer	Unknown	NA	<i>PIK3CA</i> mutations, <i>PTEN</i> mutations, or <i>PTEN</i> loss of expression	
Novartis	PKC412	Newly diagnosed acute myeloid leukemia	Unknown	NA	<i>FLT3</i> mutation	
Novartis	LDE225	Medullo-blastoma	Unknown	NA	Hh-5 gene signature	
Novartis	TKI258	Breast cancer (<i>FGFR</i> amplification), endometrial cancer (<i>FGFR</i> mutation)	Unknown	NA	<i>FGFR</i> amplification and mutation	
Novartis	MEK162	<i>NRAS</i> -	Unknown	NA	<i>NRAS</i> mutation	

Company	Pharmaceuticals	Indication	Phase of Approval or Development	Diagnostic Company	CDx Test	Source
		mutated melanoma				
Novartis	LGX818	<i>BRAF</i> -mutated melanoma	Unknown	NA	<i>BRAF</i> mutation	
Novartis	LDK378	NSCLC	Unknown	NA	<i>ALK</i> translocation	
Roche	Bitopertin	Schizophrenia (suboptimal control)	Phase III	NA	NA	Roche Annual Report 2013 ⁴¹
Roche	Gantenerumab	Alzheimer disease	Phase III	NA	A β 42 levels	
Roche	Lebrikizumab	Severe asthma	Phase III	NA	Serum periostin levels	
Roche	Pertuzumab	HER2+ early breast cancer and HER2+ gastric cancer	Phase III	NA	<i>HER2</i> expression/gene amplification	
Roche	Trastuzumab emtansine	HER2+ early breast cancer and HER2+ gastric cancer	Phase III	NA	<i>HER2</i> expression/gene amplification	
Roche	Trastuzumab emtansine \pm pertuzumab	HER2+ metastatic breast cancer (first-line)	Phase III	NA	<i>HER2</i> expression/gene amplification	
Roche	Onartuzumab	Gastric cancer	Phase III	NA	<i>MET</i> expression	
Roche	Vemurafenib	Metastatic melanoma (adjuvant therapy)	Phase III	NA	<i>BRAF</i> mutation	
Roche	Vemurafenib + cobimetinib combination	Metastatic melanoma	Phase III	NA	<i>BRAF</i> mutation	
Roche	Bcl-2 inhibitor	CLL—relapsing/refractory	Phase III	NA	NA	
Roche	Pertuzumab	HER2+ metastatic breast cancer (second-line)	Phase II	NA	<i>HER2</i> expression/gene amplification	

Company	Pharmaceuticals	Indication	Phase of Approval or Development	Diagnostic Company	CDx Test	Source
Roche	Onartuzumab	Metastatic CRC (first-line)	Phase II	NA	MET expression	
Roche	Pictilisib (<i>PI3K</i> inhibitor)	Solid tumours	Phase II	NA	NA	
Roche	Ipatasertib (<i>AKT</i> inhibitor)	Solid tumours	Phase II	NA	NA	
Roche	PDL1 MAb	NSCLC (second- and third-line)	Phase II	NA	PDL1 expression	
Roche	PDL1 MAb + Avastin	CRC	Phase II	NA	PDL1 expression	
Roche	HER3/ <i>EGFR</i> MAb	Metastatic epithelial tumours	Phase II	NA	NA	
Roche	Bcl-2 inhibitor	CLL relapsing/refractory (del[17p])	Phase II	NA	NA	
Roche	Alectinib (<i>ALK</i> inhibitor)	NSCLC	Phase II	NA	NA	
Roche	Glypican-3 MAb	Liver cancer	Phase II	NA	NA	
Roche	Etrolizumab	Ulcerative colitis	Phase II	NA	NA	
Roche	Quilizumab	Asthma	Phase II	NA	NA	
Roche	NA	CMV	Phase II	NA	NA	
Roche	FluA-MAb	Influenza	Phase II	NA	NA	
Roche	Setrobuvir	Hepatitis C	Phase II	NA	NA	
Roche	Bitopertin	Obsessive-compulsive disorder	Phase II	NA	NA	
Roche	Crenezumab	Alzheimer disease	Phase II	NA	NA	
Roche	Lampalizumab (factor D)	Geographic atrophy	Phase II	NA	CFI-expression	

Aβ42 = amyloid beta-42; *ALK* = anaplastic lymphoma receptor tyrosine kinase; *AKT* = v-akt murine thymoma viral oncogene homolog 1; *BACE* = beta-site amyloid precursor protein cleaving enzyme 1; Bcl-2 = B-cell lymphoma 2; BCR/ABL = constitutively activated tyrosine kinase inhibitors; *BRAF* = B-Raf proto-oncogene, serine/threonine kinase; CDx = companion diagnostic; CFI = complement factor I; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; CRC = colorectal cancer; CSF = cerebrospinal fluid; *EGFR* = epidermal growth factor receptor; *FGFR* = fibroblast growth factor receptor; *FLT3* = fms-related tyrosine kinase 3; HER2/HER3 = human epidermal growth factor receptor 2/3; in-house = companion tests being developed by the company developing the drug as opposed to through a commercial partner; IVD = in vitro diagnostic; MAb = monoclonal antibodies; *MET* = MET proto-oncogene, receptor tyrosine kinase; NA = information not available in the public domain; *NRAS* = neuroblastoma RAS viral (v-ras) oncogene homolog; NSCLC = non-small cell lung cancer; *P13K* = phosphoinositide 3-kinase inhibitor; PD-1 = programmed cell death protein; PD-L1 = programmed death-ligand 1; PTEN = phosphatase and tensin homolog.

^a Disclaimer: At the time this report was initially written (2014), the Web-based information sources for Janssen, Novartis, and Roche were available. However, at the time the report was revised for publication (2015), they were no longer available. Authors are therefore basing some of the information on the version of the documents printed during the preparation of the 2014 report.

Regarding global market shares, one recent study indicated that per-capita utilization of biologic personalized medicines was initially highest in the US, but that, by 2007, the per-capita utilization in five major European markets (France, Germany, Italy, Spain, and the UK) had surpassed the US. Likewise, by 2009, the per-capita utilization in Japan had also surpassed the US.⁴² Of note, information from advertisements for market research reports indicate that, currently, the largest market shares for companion diagnostics are still held by North America, followed by Europe. Asia is, however, expected to have a high growth in this market in the next few years. Because of their demographics and economies, China and India are expected to lead the growth of the companion diagnostics market in Asia.³⁵

In Canada, pCODR reports that as of December 31, 2013, there were potentially 15 individual drugs and 31 drug-indications pairs linked to 12 different companion tests on the horizon for cancer treatment.⁴³ Also on the horizon, it appears that research efforts will shift from the “one tissue, one test” to the “one tissue, many tests” concept. Indeed, as more potential targets of drugs are identified for certain cancers and more drugs requiring such tests are approved, it is anticipated that many tests may need to be run from a single (small) specimen (biopsy); tissue scarcity will become an issue in this context. For this reason, consideration is being given to developing a more comprehensive testing method that looks for all of the known genes that may be active in a tumour. Therefore, instead of using several companion tests, single platforms containing multiple genetic tests aiming to identify the underlying genetic link to a particular cancer and the best possible treatments could be used.⁴⁴ The direct-to-consumer promotion of such tests recently began in Canada.⁴⁵

Co-development and Collaboration for Companion Diagnostics

Co-development of companion diagnostics occurs when a biomarker is identified, validated, and utilized in a clinical trial alongside the investigational drug. There is also the potential economic benefit for the drug manufacturers who co-develop with a companion diagnostic — mainly that by selecting patients more likely to respond, they are able to reduce the trial enrolment and reduce the time needed to complete trials, therefore reducing the overall research costs.¹⁹

As well as co-development, there are post-market authorizations of companion diagnostics that are typically developed independently of the associated therapy and these are added to the drug label after marketing approval. These companion diagnostics are typically approved in order to optimize the use of a previously marketed therapy. For example, the effectiveness of Plavix (clopidogrel bisulfate) depends on metabolic activation by the CYP2C19 system; individuals who are treated with clopidogrel at the recommended dose but are poor metabolizers may experience higher rates of cardiovascular events following acute coronary syndrome or percutaneous coronary intervention compared with those with normal CYP2C19 function.⁴⁶ For this reason, companion diagnostic tests have been developed to identify an individual’s CYP2C19 genotype and therefore guide the treatment strategy.

Of interest, feedback was received during the stakeholder feedback period regarding the clinical development of drugs with companion diagnostics. It was mentioned that, as the knowledge of biomarkers and molecular drivers of disease increases and new research challenges are encountered (e.g., the need to screen large amounts of patients to identify those with a specific genetic mutation), there may be a shift toward smaller and alternative trial designs in precision medicine (e.g., adaptive trial designs, enrichment, and stratified clinical studies). Whether these changes will result in a positive impact on the cost of drug development, however, remains uncertain.

With respect to a collaborative model, the availability of internal diagnostics divisions within pharmaceutical manufacturers — such as at Roche, Abbott, and Novartis — does not as yet appear to represent a more favourable structure than the use of external diagnostics providers — such as at GlaxoSmithKline, Pfizer, or AstraZeneca.⁴⁷

Of note, an increase in the number of co-development and partnership agreements between pharmaceutical and diagnostic manufacturers was reported in recent years. It was found that collaboration agreements between these types of companies increased from seven in 2008 to 19 in 2009 and 25 in 2010; 34 of the 44 (77%) deals made in 2009-2010 were for oncology indications.⁴⁸

Current and Emerging Regulatory Practices

Regulatory practices for companion diagnostics are complex. The regulatory practices for companion diagnostics for three regulatory bodies of interest — Health Canada, the FDA, and the European Medicines Agency — are subsequently described.

Health Canada

In Canada, Health Canada is the department of the federal government responsible for regulating health products. Pharmaceutical products are regulated by the Therapeutic Products Directorate and biologic products are regulated by the Biologics and Genetic Therapies Directorate. IVD devices are regulated by the Therapeutic Products Directorate's Medical Devices Bureau. All devices intended to be used for pharmacogenomic testing are classified as Class III medical devices and require a pre-market scientific assessment of the safety and effectiveness by the Medical Devices Bureau.⁴⁹ Of note, medical device classification is based on the risk associated with their use; Class III devices are associated with moderate risk.⁵⁰ For new drug submissions, or a supplement to a new drug submission, involving pharmacogenomics tests (companion diagnostic tests) to support a therapeutic decision (e.g., the choice of a drug or dose), Health Canada encourages manufacturers to apply for a medical devices licence as they progress through their drug development program. If the pharmaceutical manufacturer, in its clinical trials, used a companion test that is already licensed in Canada, the manufacturer should indicate in its submission the name, description, and licence number of the IVD device that was used; however, there is no provision for joint application and review processes for the drug and the companion test.⁴⁹ Comments were received regarding the latter point during the stakeholder feedback period. These comments indicated that it may be a challenge for manufacturers to coordinate and align the review processes (so that the drug and the associated companion diagnostic test receive marketing authorization at the same time) given that the regulatory review timelines for each of these components are different.

Related to the regulatory approval of diagnostic tests, but not subject to the review by Health Canada, is the issue of quality assurance of such tests. As the number of drug treatments for which genetic testing is required increases, there is a need to ensure access to reliable high-quality testing in order to maximize the benefit that can be derived from personalized medicine. Reliability and quality of testing can be assured through establishing an effective framework for clinical laboratory operations, medical testing, and diagnostic devices. Hospitals and private laboratories offering genetic testing are subject to provincial regulations related to laboratory operations, accreditation, and quality control. Concerns have recently been expressed regarding the significant variation in the regulatory framework across the different provinces and

the lack of national oversight or guidelines in Canada to facilitate harmonization and good practice in laboratories located in all provinces.⁵¹ Of interest, during the stakeholder feedback period, comments were received on the potential need to provide information on the legal implications to Canadian health care institutions and their laboratories of using proprietary companion diagnostic tests, or equivalent laboratory-developed tests, including the on- and off-label uses of such tests.

FDA — US

The FDA typically classifies companion diagnostic tests as Class III medical devices to ensure they carry the same risk profile as the companion drug, because proper use of the diagnostic device is critical to the proper use of the drug.⁵² Class III medical devices require pre-market approval and carry the highest risk in the US regulatory system.^{5,52} Although experience indicates that most IVD companion diagnostic devices will be Class III medical devices, there may be cases when a Class II classification with pre-market notification submission (also known as a 510[k] submission) is appropriate.⁵

The FDA assesses IVD companion diagnostic testing products for safety and effectiveness. The FDA guidance includes provision for approval of companion diagnostic devices alongside novel therapeutic products and recommends that the companion diagnostic be developed and approved at the same time as the therapeutic product to ensure safe and effective use.⁵ In some instances, the FDA may approve a drug product even though the companion diagnostic is not being approved simultaneously. Under these circumstances, if the therapy demonstrates benefits “so pronounced as to outweigh the risks” from an unapproved companion diagnostic, the FDA does not delay the therapeutic product’s approval until the companion diagnostic is approved. However, the FDA expects the companion diagnostic will be subsequently approved through an appropriate IVD device submission, and that the therapeutic product label will be revised accordingly.⁵ Moreover, the FDA may consider additional measures (e.g., a risk evaluation and mitigation strategy, or a post-marketing requirement) to address any potential safety issues related to the use of the companion drug without an approved or cleared companion diagnostic test. In cases where the manufacturer intends to market an already approved or legally marketed IVD diagnostic device for another therapeutic product, the FDA requires a pre-market submission for the new use.⁵

The FDA requires the labelling of all prescription therapeutic and device products that includes information on how, when, or whether a product should be used. In the case of drugs and biological products, the label is required to include information about the following: “(1) specific tests necessary for selection or monitoring of patients who need a drug; (2) dosage modifications in special patient populations (e.g., in groups defined by genetic characteristics); and (3) the identity of any laboratory test(s) helpful in following a patient’s response or in identifying possible adverse reactions.”⁵

To ensure complete and consistent labelling for companion diagnostics and the corresponding therapy, the FDA makes a number of clarifications:

- “Information about the use of an IVD companion diagnostic device will be included in the labelling of its corresponding therapeutic product when the device meets the definition of an IVD companion diagnostic device.”⁵
- “The therapeutic product labelling should specify use of an FDA-approved or cleared IVD companion diagnostic device, rather than a particular manufacturer’s IVD companion diagnostic device. This will facilitate the

development and use of more than one approved or cleared IVD companion diagnostic device of the type described in the labelling for the therapeutic product.”⁵

- “In cases when an IVD companion diagnostic device is approved or cleared and is marketed after the therapeutic product is approved, the therapeutic product labelling should be updated to refer to the use of the IVD companion diagnostic device or type of IVD companion diagnostic device.”⁵

In the labelling of IVD companion diagnostic devices, a device intended for use with a therapeutic product must specify the therapeutic product(s) (or class of therapeutic products) with which it has been approved or cleared for use. The labelling should be amended in the following cases:

- “In some cases, if evidence is sufficient to conclude that the IVD companion diagnostic device is appropriate for use with a class of therapeutic products, the intended use/indications for use should name the therapeutic class, rather than each specific product within the class.”⁵
- “When an IVD companion diagnostic device has been approved or cleared for use with a therapeutic product in one disease or setting, a pre-market approval application (PMA) supplement or new 510(k) submission, as appropriate, will be needed to expand the IVD companion diagnostic device labelling to include additional IVD companion diagnostic device indications; e.g., use of the same therapeutic that is now approved for use in a different disease or setting.”⁵
- “When an IVD companion diagnostic device has been approved or cleared for use with one therapeutic product and evidence becomes available that use of the same device is essential for the safe and effective use of a different therapeutic product, the IVD companion diagnostic device labelling should be expanded through approval or clearance of a new pre-market submission (PMA or 510[k] as appropriate) or PMA supplement to include the new therapeutic product. Labelling of the therapeutic product should also be amended through submission of a supplement.”⁵

The final FDA guidance on IVD companion diagnostic devices (2014)⁵ also notes that these devices, when used for informing treatment decisions in clinical trials, will generally be considered investigational devices, unless the intended use of the device is already approved or cleared. The following clarifications are made regarding the use of investigational devices:

- “If used to make critical treatment decisions, such as patient selection, treatment assignment, or treatment arm, a diagnostic device generally will be considered a significant risk device under 21 CFR 812.3(m)(3) because it presents a potential for serious risk to the health, safety, or welfare of the subject, and the sponsor of the diagnostic device will be required to comply with the investigational device exemption (IDE) regulations that address significant risk devices.”⁵
- “If a diagnostic device and a therapeutic product are to be studied together to support their respective approvals (or clearance as appropriate for the diagnostic device), both products can be studied in the same investigational study, if the study is conducted in a manner that meets both the requirements of the IDE regulations (21 CFR Part 812) and the investigational new drug (IND) regulations (21 CFR Part 312). Depending on details of the study plan and participants, a sponsor may seek to submit an IND alone, or both an IND and

an IDE. Sponsors should consult with the therapeutic product center and the relevant device center as to which approach is best or necessary for a particular study.”⁵

To help the FDA process investigational submissions and understand how the IVD companion diagnostic devices will be validated and used to enrol patients, submissions should include key information about the planned use of a companion diagnostic device in the clinical trial(s). The FDA also promotes the participation of both diagnostic device manufacturers and pharmaceutical manufacturers in discussions about the proposed IVD companion diagnostic devices and feedback solicitation from the FDA through the pre-submission process to help in planning for a device PMA or 510(k) submission that is complete and timely.⁵

The FDA also informed the United States Congress (July 31, 2014) that it would issue, in 60 days, its draft guidance on laboratory-developed tests (LDTs).^{53,54} This FDA initiative could affect 2,000 laboratories in the US⁵³ and was prompted by the desire to ensure that LDTs are accurate and reliable. The proposed framework defines an LDT as an IVD that is intended for clinical use and is designed, manufactured, and used within a single laboratory. Although the proposed framework will apply to all LDTs, it is mentioned that companion diagnostics will be considered high-risk Class III LDTs, which means that laboratories manufacturing these tests will be subjected to submitting a pre-market submission within 12 months from issuance of the final FDA guidance.⁵⁴ The draft guidance, entitled *Framework for Regulatory Oversight of Laboratory Developed Tests (LDTs) Draft Guidance* was distributed for comment on October 3, 2014.⁵⁵

European Medicines Agency — Europe

In Europe, the regulatory framework consists of three directives: active implantable medical devices (Directive 90/395/EEC), medical devices (Directive 93/42/EEC), and in vitro medical devices (Directive 98/79/EC). Currently, the regulation of IVD medical devices falls under the Directive of the European Parliament and of the Council (“the IVD Directive”).⁵⁶ Under this regulatory framework, IVD devices are not subject to pre-market authorization by a regulatory authority. They are instead subject to a conformity assessment, which is the sole responsibility of the manufacturer for the majority of medical devices⁵⁶ — although for high-risk devices and devices for self-testing, an independent third party is required for the conformity assessment. Once certified, medical devices are allowed to circulate freely in the European Union (EU) or European Free Trade Association countries and Turkey.⁵⁶

Proposed regulations will follow guidance put forth by the Global Harmonization Task Force, in which companion diagnostics will be classified as high-risk, or as Class C, medical devices. As Class C devices, companion diagnostic devices must be assessed by the independent third party before the certification is issued.⁵⁷ The proposed regulations also provide some clarification for the regulation of new therapeutic products requiring a companion diagnostic. The proposal provides for a consultation with the EMA, or a competent authority in the case of companion diagnostics devices, concerning the “suitability of the companion diagnostic in relation to the safe and effective use of the medicinal product in question.”⁵⁶ At the time of this update, the proposal was reported to be “awaiting council 1st reading position/budgetary conciliation convocation”.⁵⁸

The proposed regulations stipulate that the independent third parties assessing companion diagnostics must consult the EMA or an individual national competent authority for evaluation of the suitability of the companion diagnostic in relation to the therapy concerned. The EMA consultation includes a review of the draft summary of clinical safety and efficacy, as well as instructions for use; however, the purpose or benefit of the EMA review is unclear, and any steps to resolve discrepancies between the EMA and third-party assessments are also lacking.⁵⁷

There is little publicly available information on companion diagnostics and their therapeutics, as made evident in a statement from a 2012 communication regarding the proposed regulation changes: “to ensure transparency, in particular through an expanded European database on medical devices and in vitro diagnostic medical devices partially accessible to the public. It will provide patients, health care professionals and the public at large with comprehensive information on products available on the EU market, enabling them to make better informed decisions.”⁵⁹

The key market requirements for companion diagnostic tests seeking regulatory approval in Canada, the US, and the EU are listed in Table 5. As described previously, although guidance documents are available in the public domain, there was a lack of publicly available information from Canada and the EU on the specific regulatory requirements pertaining to drugs requiring a companion diagnostic test to create a complementary table for drug products.

Table 5: Comparison of Key Market Requirements for Companion Diagnostics (Adapted from Ansari, 2013⁵²)

	CANADA	US	EU
Regulatory Body	Health Canada	FDA	Competent authority ^a
Class	III	III	Self-certification, non-Annex A/B
Application	Medical Devices Licence Application	Pre-market approval application	Technical documentation
Performance Evaluation	✓	✓	✓
Clinical Trial	✓	✓	X
Regulatory Review Time	75 days ^b	180 days	NA

Source: Ansari, M., *Therapeutic Innovation & Regulatory Science* (July 2013, vol. 47, no. 4: 405-415)

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EU = European Union; FDA = Food and Drug Administration; NA = information not available; US = United States.

^a Based on legal manufacturer's physical location.

^b Performance review target to first decision (60 days) + submission screening phase (15 days).⁶⁰

Current and Emerging Reimbursement Practices

Reimbursement policies and practices for companion diagnostics are not well-defined. Both government and private payers in the countries subsequently listed typically utilize health technology assessments (HTAs) to inform their evaluations of clinical and economic benefits associated with pharmaceuticals. Comparative effectiveness research (CER) is also utilized to compare outcomes of novel technologies (including their coverage and payment) to relevant comparators (such as established standards of care). The evidence presented in the HTA and/or CER typically provides the basis for reimbursement and coverage decisions for pharmaceuticals. Standardized methods for determining clinical utility and reimbursement rates for diagnostic tests are

lacking; therefore, coverage and reimbursement rates are often set on a case-by-case basis. At this time, individual payers seem to determine what evidence is required for companion diagnostics to show improvement in patient outcomes and cost-effectiveness.⁶¹

Reimbursement policies for pharmaceutical products are usually developed by drug plans. In Canada, publicly funded drug plans are managed at the federal, provincial, and territorial levels. In most cases, the public payers (i.e., public drug plans and cancer agencies) base their reimbursement decisions on recommendations from the major drug review bodies across Canada (i.e., CADTH's Canadian Drug Expert Committee [CDEC] and pCODR Expert Review Committee [pERC]). The reimbursement model for pharmaceuticals may differ in other countries. Regarding the funding of companion diagnostic tests — given that there is a lack of information available in the public domain — it is unknown whether publicly funded drug programs currently reimburse these tests and, if they do, what reimbursement model is used. Additional information is available in the sections that follow.

Canada

Once a pharmaceutical product has been authorized for sale through a Health Canada review (which assesses evidence about a drug's safety, clinical efficacy, and the quality of its manufacturing process), the manufacturer must formally submit that product for a HTA in order to obtain approval for reimbursement on publicly funded drug plans. In Canada, CADTH has two programs which undertake HTA assessment: the Common Drug Review (CDR) and pCODR, depending on whether the product is a non-cancer drug or a cancer drug, respectively. These programs assess the drug by reviewing scientific evidence on its comparative clinical and economic effectiveness. Expert committees then develop recommendations to inform reimbursement decisions at the jurisdictional level.⁶² Of note, pCODR was established in 2010 by Canada's provincial and territorial Ministries of Health (with the exception of Quebec). pCODR has been part of CADTH since April 2014.⁶³

Regarding drugs, jurisdictional drug plans and cancer agencies use the pERC and CDEC recommendations in conjunction with input from their own expert committees to consider the effect on health services and overall budget to determine whether a drug will be funded.⁶² As previously stated, pCODR has completed 13 reviews of targeted therapies for cancer treatment as of the end of 2015.²⁵ Appendix 3 describes the drug reimbursement process at the federal, provincial, and territorial levels; however, at this time, no specific reimbursement policies for companion drugs and associated diagnostics have been identified from any of the provincial bodies. In addition to these publicly funded drug plans, private insurance is also available in Canada to assist with costs related to prescription drugs.^{64,65}

For companion drugs and diagnostics, pERC recently recommended the funding of panitumumab (Vectibix) in addition to combination chemotherapy, conditional on cost-effectiveness being improved to an acceptable level, for the treatment of patients with non-mutated wild-type *RAS* metastatic colorectal cancer.⁶⁶ Recommendations on non-oncology companion drug products are also possible. For example, CDEC⁶⁷ recently recommended that ivacaftor (Kalydeco) be listed for the treatment of cystic fibrosis in patients aged six years and older who have a G551D mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene. Part of this recommendation means that cystic fibrosis patients will have to be screened to determine their status regarding G551D mutation in the *CFTR* gene before accessing this treatment. This

requirement is also included in the product monograph, although no specific laboratory test is described for that purpose.⁶⁸

These examples illustrate the dependency between the accessibility to certain drugs and the accessibility to specific genetic tests. Concerns have recently been expressed regarding the potential for disjointed approval and funding processes for pharmaceuticals and companion tests. Regarding funding decisions for genetic tests, these are made at the provincial level; decisions may vary across jurisdictions. However, some provinces may not have dedicated processes in place to review, fund, and implement such tests. These situations may result in increased pressure on individual hospitals to evaluate and offer new genetic tests; when the local decision is made to offer the test, usually it is done without additional funding. These independent hospital-based decisions may result in considerable duplication of effort and prevent standardization of policies across institutions. Sometimes, when jurisdictional funding is lacking, pharmaceutical companies may offer to cover for the cost of companion tests. This approach is based on the anticipated return on investment when new patients become candidates for the drugs sold by the company. While such an approach allows health ministries and hospitals to save money on genetic testing, funding from industry may be limited in time or associated with conditions in the utilization of the test. In that context, funding for a companion diagnostic test associated with a particular drug may be limited to patients qualifying for therapy with this specific drug, as the latter is sold by the manufacturer providing funding for the test. These situations lead to confusion for patients and clinicians regarding the availability of genetic tests and may result in inequities regarding the availability of such tests.⁵¹ Comments received during the stakeholder feedback period indicated support for a centralized structure for the funding of companion diagnostics in order to ensure quality of tests and consistency in patient access to this technology across Canada.

US

Both government and private payers in the US utilize HTA and CER to inform their evaluation of clinical and economic benefit associated with pharmaceuticals, which provides the basis for reimbursement and coverage decisions.⁶⁹ Reimbursement for diagnostics can be slightly different in that pricing is often benchmarked to the Medicare Clinical Laboratory Fee Schedule, although other approaches (e.g., direct payment negotiation with payers) sometimes occur.⁶⁹

In the case of IVDs, determination of reimbursement may involve two or more stakeholders to evaluate the value of the test by developing and communicating evidence. In addition to HTA findings regarding efficacy, payers also consider “the clinical utility of novel diagnostics attempting to understand (through data) how the novel diagnostic will impact clinical pathways, treatment decisions, prognosis, and ultimately outcomes. Lack of evidence related to clinical impact can limit coverage.”⁶⁹ This information can be used to determine coverage and payment for the IVD, although reimbursement policies may vary widely across payers and products, as these decisions are payer-specific. The HTA process is decentralized for both private and public payers, and varies across payers, who typically have a technology assessment committee. In addition to these HTA committees, payers may also utilize third-party HTA organizations to provide evidence-based reviews and rate the evidence to help inform decision-making by the payer.⁶⁹

Medicare and Medicaid

No reimbursement policies for companion diagnostics were identified from either the Medicare or Medicaid websites. An external source⁶⁹ noted that Medicare “can create national or local coverage policies; however, most diagnostics are paid without explicit policies.” In addition, the same source noted that, for Medicaid, “each state sets its own guidelines regarding eligibility, services, and reimbursement.”⁶⁹

US Department of Veterans Affairs

The Veterans Affairs (VA) Health Services Research & Development program is a national program tasked with “identifying and evaluating innovative strategies that lead to accessible, high quality, cost-effective care for Veterans and the nation”.⁷⁰ Companion diagnostics would fall under the “genomic medicine” assessed.⁷¹ The VA also has some personalized medicine research initiatives such as the Precision Oncology Program ; however, no explicit policies were identified from the website.⁷²

Private Payers

In the US, there are also many private payers who provide specific coverage and payment to their health plan members. Companion diagnostics would be covered under the medical benefits of these health plans, and the coverage and reimbursement of these devices or therapies would be reviewed within each organization.⁶⁹

United Kingdom

In the UK, companion diagnostics are considered by NICE, which dispenses guidance to the National Health Service (NHS) for England and Wales on the clinical and cost-effectiveness of health technologies (Scotland and Northern Ireland have separate reimbursement bodies). Reflecting the two clinical development paths for such tests, NICE provides guidance on companion diagnostics through one of two programs:^{13,73}

- Tests linked to new drugs are appraised through the Technology Appraisal Programme (TAP), as part of the appraisal of the new drugs.
- Tests linked to established drugs follow the Diagnostics Assessment Programme (DAP).

Both of these programs utilize quality-adjusted life-years (QALYs) to compare the clinical and cost-effectiveness across technologies.¹² More information follows.

Technology Appraisal Programme

In the UK, new pharmaceuticals (including companion diagnostics) are evaluated through the NICE Technology Appraisal Programme (TAP) when these technologies are developed in parallel.^{13,73,74} This program establishes the added value of the medicine component rather than the predictive value associated with the companion diagnostic being used to select the eligible population for treatment.²¹ The guide to the methods of TAP was updated in 2013.⁷⁵ A recent publication explains that the purpose of the updated guidelines on companion diagnostics is to mitigate any delays in the appraisal of the associated therapy.¹² The new guidelines stipulate that manufacturers should include the costs of the companion diagnostic in the estimates of cost-effectiveness for the associated companion pharmaceutical; a sensitivity analysis for cost-effectiveness in which the costs of testing are excluded should also be conducted.¹² The new process is thought to provide clarity on the impact of the companion diagnostic on the cost-effectiveness of the associated therapy.¹² Finally, the new guidance also allows for issues associated with the potential use of alternative tests to be mentioned without the identification or consideration of evidence for those tests.¹²

Diagnosics Assessment Programme

Diagnosics that already have a Conformité Européenne (CE) mark and are considered to be additions to a current treatment pathway are directed through the Diagnostic Assessment Programme (DAP)²¹ (note that a CE mark is required for marketing a medical device in Europe). In this program, NICE may be notified by sponsors (including manufacturers and clinical communities) of companion diagnostic products, which may then be selected for evaluation through DAP, as deemed appropriate. Through this process, the various clinical diagnostic options can be included in the assessment (i.e., other proprietary and “in-house” tests), and cost-effectiveness determinations for each pharmaceutical and clinical diagnostic combination may be examined.⁷⁴ The DAP program is used to evaluate the clinical and cost-effectiveness of these diagnostic technologies, the diagnostic accuracy, the impact of the diagnostic on clinical decisions, and the impact of these decisions on patients. In addition, guidance is issued for the use of the diagnostic within the NHS.¹²

Table 6 describes the appraisal guidance on pharmaceuticals with companion diagnostics published by NICE between 2003 and 2013.

Table 6: Published NICE Technology Appraisal Guidance of Pharmaceuticals with Companion Diagnostics¹²

NICE Guidance Report Number	Appraisal Title	Marker	Date Published
TA70	Imatinib for the treatment of chronic myeloid leukemia (partially updated by TA241 and TA251)	Philadelphia chromosome (genetic marker)	October 2003
TA107	Trastuzumab for the adjuvant treatment of early-stage HER2-positive breast cancer	HER2 (protein marker)	March 2002
TA118	Bevacizumab and cetuximab for metastatic colorectal cancer	EGFR (protein marker)	January 2007
TA176	Cetuximab for the first-line treatment of metastatic colorectal cancer	<i>KRAS</i> (genetic marker)	August 2009
TA192	Gefitinib for the first-line treatment of locally advanced or metastatic non-small cell lung cancer	<i>EGFR</i> -TK mutations (genetic marker)	July 2010
TA208	Trastuzumab for the treatment of HER2-positive metastatic gastric cancer	HER2 (protein marker)	November 2010
TA241	Dasatinib, high-dose imatinib, and nilotinib for the treatment of imatinib-resistant CML, and dasatinib and nilotinib for people with CML for whom treatment with imatinib has failed because of intolerance	Philadelphia chromosome (genetic marker)	January 2012
TA251	Dasatinib, nilotinib, and standard-dose imatinib for the first-line treatment of CML	Philadelphia chromosome (genetic marker)	April 2012

NICE Guidance Report Number	Appraisal Title	Marker	Date Published
TA258	Erlotinib for the first-line treatment of locally advanced or metastatic <i>EGFR</i> -TK mutation-positive, non-small cell lung cancer	<i>EGFR</i> -TK mutations (genetic marker)	June 2012
TA269	Vemurafenib for treating locally advanced or metastatic <i>BRAF</i> V600 mutation-positive malignant melanoma	<i>BRAF</i> V600 mutation (genetic marker)	December 2012
TA296	Crizotinib for treating adults with previously treated <i>ALK</i> -positive, advanced non-small cell lung cancer	<i>ALK</i> (genetic marker)	September 2013

Source: Reprinted from *Clinical Cancer Research*, 2014, Volume 20, Issue 6, 1469-76. Byron SK, Crabb N, George E, Marlow M, Newland A. The health technology assessment of companion diagnostics: experience of NICE, Table 1, p. 1473, with permission from AACR. *ALK* = anaplastic lymphoma receptor tyrosine kinase; *BRAF* = B-raf proto-oncogene, serine/threonine kinase; CML = chronic myeloid leukemia; *EGFR* = epidermal growth factor receptor; *HER2* = human epidermal growth factor receptor 2; *KRAS* = Kirsten rat sarcoma viral oncogene homolog; NICE = National Institute for Health and Care Excellence; TK = tyrosine kinase.

Table 7 provides a list of examples of United Kingdom and US public and private reimbursement policies for companion diagnostic tests.

Table 7: Reimbursement Policies (Meckley and Neumann, 2010⁴)

Personalized Medicine Test	NICE	Aetna	Cigna	Premera (BC) ^a	CMS
CYP2C9/VKORC1 testing	No policy	No ^b	Yes	No ^b	CED ^c
Hepatitis C genotyping	Yes	Yes ^d	Yes ^d	Yes ^d	Yes
HER2 testing	Yes	Yes ^e	Yes ^e	Yes ^e	Yes
UGT1A1 testing	No policy	No ^b	No ^b	No policy	No policy
Oncotype DX	Under consideration	Yes	Yes	Yes	Yes
BRCA1/BRCA2 testing	Yes ^f	Yes ^g	Yes	Yes	Yes ^h

Source: Reprinted from Health Policy, volume 94, issue 2, Meckley LM, Neumann PJ. Personalized medicine: Factors influencing reimbursement, pages 91-100, 2010 Feb (© 2009), Table 2, p. 94, with permission from Elsevier.

CED = coverage with evidence development; CMS = Centers for Medicare & Medicaid Services; *HER2* = human epidermal growth factor receptor 2; NICE = National Institute for Clinical Excellence (UK).

^a Blue Cross.

^b Test is considered experimental.

^c Coverage with evidence development.

^d Pegylated interferon coverage time varies by genotype.

^e Trastuzumab only covered in *HER2*+ women.

^f *BRCA1/BRCA2* testing only covered in women with breast cancer or relatives of women who test positive.

^g Coverage based on guidelines.

^h Covered only in breast or ovarian cancer patients.

Australia

In late 2010, acknowledging the need to improve current models of assessing personalized medicine to inform reimbursement decisions and provide clarity to industry regarding policy-makers' expectations, the Australian Government Department of Health and Ageing (now the Department of Health) released the first integrated national framework for reviewing codependent technologies (defined as biomarker, test, and drug packages).⁷⁶ This framework^{76,77} includes five components:

- Section A: Context for the submission
- Section B: Clinical benefit, effectiveness, and safety of the pair of codependent technologies
- Section C: Can the test-drug evidence of effectiveness be translated to an economic model for the Australian clinical setting?
- Section D: Is the proposed use of the pair of codependent technologies cost-effective?
- Section E: What is the financial impact of the proposed listing of the pair of codependent technologies?

A checklist of 79 items is also included in the framework.^{76,77} This framework was developed to assess joint submissions of new codependent technologies, in which case all 79 items of the checklist need to be addressed. However, the framework provides flexibility to evaluate codependent technologies in other situations; e.g., evaluating a submission for a new drug targeting a previously validated biomarker for which a companion test is already being reimbursed. In the latter case, it would be inefficient to address all 79 items of the checklist. In addition, the framework includes consideration of the type of evidence supporting the efficacy of the codependent technologies; there are five different levels of evidence, including “direct” evidence (ranging from the ideal trial design [i.e., double randomized controlled trials, level 1 evidence] to “linked” evidence [level 5 evidence; i.e., linking evidence from studies conducted in different populations]).^{76,77} Of note, although this framework was developed for the Australian health system, it is anticipated that it may be a suitable model for other health systems.⁷⁶

New Zealand

In New Zealand, the Pharmaceutical Management Agency manages District Health Boards’ hospital expenditures on pharmaceutical cancer treatments (PCTs) through the Pharmaceutical Schedule; it also determines access criteria for PCTs. Therefore, patients admitted to hospitals in New Zealand should have equal access to PCTs. Any therapies not on the published list of PCTs will not be accessible by District Health Boards without an application under the Named Patient Pharmaceutical Assessment policy.⁷⁸ Similar to Canada, no formal policies or processes were identified for the reimbursement of companion drugs and associated diagnostics.

Potential Financial Impact, Particularly on Public Payers

Increasing demands are being placed on manufacturers to establish the cost-effectiveness of their products in the allocation of finite, and often limited, health care budgets. By allowing providers to predict which patients will respond to therapy, companion diagnostics may help to reduce health care costs.⁴⁸ However, whether there will actually be a positive impact on health care costs is uncertain, given the still-limited deployment of this new technology in routine clinical practice.

Specific examples of cost-savings come from recent reports indicating that for patients with metastatic colorectal cancer, approximately \$600 million could be saved annually if Vectibix or Erbitux were limited to patients with the wild-type *KRAS* gene.¹² In addition, companion diagnostics may reduce adverse drug reactions by preventing the prescription of certain treatments to those individuals with specific biomarkers, thereby reducing the potential costs for medical attention or hospitalization.¹² As previously noted, in order to demonstrate the more cost-efficient delivery of care associated with the broader deployment of pharmaceuticals with companion diagnostics, further

scientific evidence and practice-based data of such potential financial benefits are required.

The potential impact of introducing a new companion diagnostic medicine as a combination technology also has the complexity of affecting budgets for both laboratory and pharmacy services. In private health care systems, such as some of those operating in the US, the introduction of a new companion diagnostic test associated with a particular drug therapy results in the need for the provider to charge additional fees for performing the test.²¹ In a publicly funded health system, the introduction of the companion test is associated with additional costs for the laboratories. Of interest, during the stakeholder feedback period, comments were received concerning the latter point. Concerns were raised regarding the proprietary nature of the companion diagnostic tests and the potentially higher resulting costs to laboratories and funding agencies. It was mentioned that laboratories should have the opportunity to choose how they will test for a genetic variation after demonstrating equivalent sensitivities with the test used in clinical trials. This practice could lead to laboratories developing more tests in-house; alternatively, laboratories could choose other commercial molecular assay kits that test for the same mutation as the testing kit used in the clinical trials should other manufacturers commercialize such tests at a lower price. Table 8 provides an example of the costs associated with the targeted therapy and the associated companion diagnostic test.

Table 8: Cost of Therapy and Associated Companion Diagnostics Tests in US Dollars⁴⁷

Pharmaceutical	Annual Cost	CDx	Test Cost
Xalkori (crizotinib, Pfizer)	\$115,200	Vysis ALK Break Apart FISH Probe Kit (Abbott Molecular)	\$1,500
Zelboraf (vemurafenib, Plexxikon/Daiichi-Sankyo/Roche)	\$56,400	Cobas 4800 BRAF V600 Mutation Test (Roche Molecular Diagnostics)	\$120 to \$150
Herceptin (trastuzumab, Genentech/Roche)	\$70,000	HercepTest (Dako)	\$500

Source: Adapted from Blair ED, Stratton EK, Kaufmann M. Aligning the economic value of companion diagnostics and stratified medicines. *J Pers Med.* 2012 Nov 26;2(4):257-66. Table 1, p. 261.

ALK = anaplastic lymphoma kinase; BRAF = B-raf proto-oncogene, serine/threonine kinase; CDx = companion diagnostic; FISH = fluorescence in situ hybridization.

A recent report indicated that the drive toward developing required companion diagnostic tests is due in part to payers, who are demanding increased evidence of cost-effectiveness before reimbursing treatments.¹² One study that looked at specific diagnostic tests identified a number of examples of companion diagnostics associated with either cost-saving or reasonable cost-effectiveness ratios; e.g., less than \$50,000/QALY (see Table 9).⁴

Table 9: Examples of Cost-Attractive Companion Diagnostic Tests (Adapted from Meckley and Neumann, 2010⁴)

Personalized Medicine Test (Therapy)	Purpose	FDA Label Includes Test	Cost-Effectiveness of Test Use ^a
HER2 testing (trastuzumab)	Disease differentiation	Yes	\$8,000 to \$30,000/QALY ⁷⁹
Hepatitis C genotyping (pegylated interferon and ribavirin)	Disease differentiation	Yes	\$7,500/QALY ⁸⁰
Oncotype DX (adjuvant chemotherapy)	Disease differentiation/ genetic predisposition	Not included	Cost-saving: \$1,944/QALY ^{81,82}
UGT1A1 testing irinotecan	Pharmacogenetics	Yes	Cost-saving ⁸³

Source: Reprinted from *Health Policy*, volume 94, issue 2, Meckley LM, Neumann PJ. Personalized medicine: Factors influencing reimbursement, pages 91-100, 2010 Feb (© 2009), Table 3, p. 95, with permission from Elsevier.

HER2 = human epidermal growth factor receptor 2; QALY = quality-adjusted life-year. ^a Currency is US \$.

Conclusion

Companion diagnostics are IVD tests designed to provide information on the presence or absence of biomarkers that can influence treatment pathways for patients. For instance, the detection of biomarkers allows prescribers to identify subpopulations of patients who will most likely benefit from a particular therapy, or who are more susceptible to adverse drug reactions for a particular therapy. Although the majority of therapies with a required companion diagnostic available globally are for oncology indications, other therapies for disease areas such as HIV, rheumatoid arthritis, and hepatitis C have also been approved for use with a companion diagnostic test.

The global market for companion diagnostics is expected to grow considerably until the end of this decade, with CAGR around 20%. Based on preliminary information, the CAGR for the market composed of targeted therapies and companion diagnostics may be estimated to be between 9% and 10%. The co-development of companion diagnostics and new drugs therapies, as well as the partnership between diagnostic and pharmaceutical companies, may be strategies that will be increasingly adopted to capture part of this growing market.

The national and international (US and EU) regulatory processes for the approval of companion diagnostics and associated therapies were explored as part of this Environmental Scan. The FDA had the most developed and detailed process available online, including the recently released 2014 guidelines, which promote both the co-development and joint approval of companion drugs and diagnostics. The EMA is drafting revisions to its existing regulations, with the expectation of more defined regulations for the development and approval of companion diagnostics and associated therapies. In the UK, two distinct strategies are in place to evaluate companion diagnostics, depending on whether these are developed jointly with the targeted therapy, or whether they are developed at different times. In Canada, although there is no provision for joint application and review of drugs and their companion tests, Health Canada encourages manufacturers intending to use such tests to apply for a medical licence as they progress through their drug development program.

In terms of reimbursement, this Environmental Scan has found the processes in Canada, the US, and New Zealand to be less definitive compared with countries like the UK and Australia. In Canada and the US, reimbursement is a decentralized

process; therefore, recommendations for funding of pharmaceuticals to public payers are provided by national bodies (for example, in Canada, recommendations are made by pERC and CDEC), while decisions regarding the funding of drugs, as well as devices, are made at the jurisdictional (i.e., federal, provincial, and territorial) levels. In the UK, NICE has established a formal set of guidelines for the appraisal of companion diagnostics and associated therapies. In late 2010, acknowledging the need to improve current models of assessment of personalized medicine to inform reimbursement decisions and provide clarity to industry regarding policy-makers' expectations, Australia launched the first fully integrated national framework to inform funding decisions for drugs with companion diagnostics.

Within the Canadian context, particularly with respect to the oncology setting, concerns have recently been expressed regarding cross-jurisdictional inconsistency in the processes to approve, fund, and access genetic tests. Another important issue raised was the lack of standardization in the quality assurance of these tests (which is performed in different laboratories in Canada).

In the future, pharmaceutical and diagnostic companies are expected to increasingly collaborate, develop, and market diagnostic tests for pipeline therapies. Although some pharmaceutical companies have in-house capabilities, many depend on collaborations or partnerships with diagnostic companies to develop companion diagnostics for their therapies: the number of agreements between pharmaceutical and diagnostic companies was noted to have increased in recent years.

The most important factor contributing to the growth of companion diagnostics is the increasing scientific understanding of disease at the molecular level, and the discovery of links between genetic mutations or biomarkers and the efficacy and/or safety of drugs. Another growth driver is the potential research advantage for drug manufacturers, who may be able to reduce their research costs by targeting patients more likely to respond to their product in development; this could possibly result in manufacturers needing to enrol fewer patients in clinical trials. The anticipated attractive cost-effectiveness of therapies requiring companion diagnostics may be another driver of the growth in this area, because of the potential for cost-savings on several fronts. The first cost-saving potential is limiting the therapy to only subpopulations in which the drug has been proven to be effective. The second cost-saving is the reduction of adverse reactions to the drug by identifying populations who might be more susceptible, and thereby minimizing the health care costs associated with the management of the adverse reactions. Overall, the cost of the diagnostic test is relatively small (e.g., HercepTest is US\$500) compared with the typical cost of the associated therapy (e.g., the annual cost of Herceptin is US\$70,000). It may therefore be anticipated that an increase in potential changes in labelling by regulatory bodies from "recommended" to "required" for companion diagnostic tests may not have a major impact on publicly funded drug program budgets in light of the potential cost-savings, provided the clinical use of these technologies reflects best practices. A Canadian budget impact analysis would, however, be required to validate such a preliminary observation. In addition, in order to demonstrate the more cost-efficient delivery of care potentially associated with the broader deployment of pharmaceuticals with companion diagnostics, further scientific evidence and practice-based data will be required. Therefore, until such data are available and the clinical development and deployment of pharmaceuticals with companion diagnostics expand, it remains uncertain whether the expanded use of these codependent technologies will lead to more cost-efficient clinical development and delivery of care.

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Appendix 1: Approved Pharmaceuticals With An Associated Companion Diagnostic Test

Table 10: Pharmaceuticals Requiring Diagnostic Tests

Drug Trade Name (Generic Name) and Associated Companion Diagnostic Test ⁸⁴	Tumour Type/Indication ^a	Health Canada	FDA	EMA
		Year of Approval ⁸⁵	Year of Approval ⁸⁶	Year of Approval
Erbix (cetuximab) Therascreen KRAS RGQ PCR Kit Dako EGFR pharmDx Kit	Gastrointestinal; metastatic colorectal cancer ^{84,87}	September 2005	2004	2004 ⁸⁸
Vectibix (panitumumab) Dako EGFR pharmDx Kit	Colorectal cancer ⁸⁴	April 2008	2006	2007 ⁸⁸
Exjade (deferasirox) FerriScan	Non–transfusion-dependent thalassemia	October 2008	2005	2006 ⁸⁸
Giotrif/Gilotrif (afatinib) Therascreen EGFR RGQ PCR Kit	Advanced non–small cell lung cancer ⁸⁷	November 2013 Note: Brand name in Canada is Giotrif	2013	
Gleevec/Glivec (imatinib mesylate) Dako c-Kit pharmDx	GIST ⁸⁴	September 2001 Note: Brand name in Canada is Gleevec. Generic versions are also available in Canada under the trade name Teva-imatinib and Apo-imatinib	2003	2001 ⁸⁸
Herceptin (trastuzumab) INFORM HER2/neu PathVysion HER2 DNA Probe Kit PATHWAY ANTI-HER2/neu (4B5) Rabbit Monoclonal Primary Antibody InSite HER2/neu Kit SPoT-Light HER2 CISH Kit BOND Oracle Her2 IHC System HER2 CISH pharmDx Kit INFORM HER2 Dual ISH DNA Probe Cocktail HER2 FISH pharmDx Kit HercepTest	Breast cancer ⁸⁴	August 1998	1998	2000 ⁸⁸
Kadcyla (ado-trastuzumab emtansine) HER2 FISH pharmDx Kit	Metastatic breast cancer ⁸⁷	September 2013	2013	2013 ⁸⁸

Drug Trade Name (Generic Name) and Associated Companion Diagnostic Test ⁸⁴	Tumour Type/Indication ^a	Health Canada	FDA	EMA
		Year of Approval ⁸⁵	Year of Approval ⁸⁶	Year of Approval
Perjeta (pertuzumab) HercepTest HER2 FISH pharmDx Kit	Metastatic breast cancer ⁸⁹	April 2013	2012	2013 ⁹⁰
Mekinist (trametinib) THxID-BRAF Kit	Melanoma; metastatic melanoma ⁸⁷	July 2013	Approved as single drugs in 2013, and in combination in 2014 ⁹¹	Request for combined use: Withdrawn Mekinist: Review under way ⁹² Tafinlar - 2013 ⁸⁸
Tafinlar (dabrafenib) THxID-BRAF Kit	Melanoma; metastatic melanoma ⁸⁷	July 2013		
Tarceva (erlotinib) cobas EGFR Mutation Test	Metastatic non-small cell lung cancer ⁸⁴	July 2005	2004	2005 ⁸⁸
Xalkori (crizotinib) Vysis ALK Break Apart FISH Probe Kit	Advanced non-small cell lung cancer ⁸⁷	April 2012	2011	2012 ⁸⁸
Zelboraf (vemurafenib) cobas 4800 BRAF V600 Mutation Test	Melanoma; advanced melanoma ⁸⁷	February 2012	2011	2012 ⁸⁸
Vynfinit (vintafolide) Companion imaging drugs Folcepri (etarfolatide) and Neocepri (folic acid)	Platinum-resistant ovarian cancer ⁹³	Not available in Canada	Granted orphan drug status; date NR ⁹⁴	2014 ⁹³
Kalydeco (ivacaftor)	Treatment of cystic fibrosis in patients aged 6 years and older who have a G551D mutation in the <i>CFTR</i> gene ⁹⁵	November 2012	2012	2012 ⁸⁸

ALK = anaplastic lymphoma kinase; CISH = chromogenic in situ hybridization; CFTR = cystic fibrosis transmembrane conductance regulator; CML = chronic myeloid leukemia; EGFR = epidermal growth factor receptor; EMA = European Medicines Agency; FISH = fluorescence in situ hybridization; GIST = gastrointestinal stromal tumour; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemical; KRAS = Kirsten rat sarcoma viral oncogene homolog; NR = not reported; PCR = polymerase chain reaction.

^a Indications may vary, depending on the decisions made by the country or jurisdiction where the companion tests were approved for use.

Appendix 2: Approved Companion Diagnostic Tests

Table 11: Commercially Available Diagnostic Tests Licensed for Use with Companion Drugs

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
Therascreen KRAS RGQ PCR Kit Erbix (cetuximab)	The Therascreen KRAS RGQ PCR Kit is a real-time, qualitative, PCR assay used on the Rotor-Gene Q MDx instrument for the detection of seven somatic mutations in the human <i>KRAS</i> oncogene, using DNA extracted from FFPE CRC tissue. The Therascreen KRAS RGQ PCR Kit is intended to aid in the identification of CRC patients for treatment with Erbitux (cetuximab) based on a <i>KRAS</i> no-mutation-detected test result. ⁸⁴	Approved Type: Test Kit Device Class: III First Issue Date: 2009-05-08 Licence Name: TheraScreen: K-RAS Mutation Kit	Approved	Approved ⁹⁷
Dako EGFR pharmDx Kit Erbix (cetuximab); Vectibix (panitumumab)	The EGFR pharmDx assay is a qualitative IHC kit system to identify EGFR expression in normal and neoplastic tissues routinely fixed for histological evaluation. EGFR pharmDx specifically detects the EGFR (HER1) protein in EGFR-expressing cells. EGFR pharmDx is indicated as an aid in identifying CRC patients eligible for treatment with Erbitux (cetuximab) or Vectibix (panitumumab). ⁸⁴	Approved Type: Test Kit Device Class: II First Issue Date: 2004-11-23 Licence Name: EGFR pharmDX Kit	Approved	Approved ⁹⁸
FerriScan Exjade (deferasirox)	The FerriScan R2-MRI Analysis System is intended to measure liver iron concentration to aid in the identification and monitoring of non-transfusion-dependent thalassemia patients receiving therapy with deferasirox. ⁸⁴	NA	Approved	Approved ⁹⁹
Therascreen EGFR RGQ PCR Kit Giotrif/Gilotrif (afatinib)	The Therascreen EGFR RGQ PCR Kit is a real-time PCR test for the qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the EGFR gene in DNA derived from FFPE NSCLC tumour tissue. The test is intended to be used to select patients with NSCLC for whom Giotrif/Gilotrif (afatinib), an EGFR TKI, is indicated. Safety and efficacy of Giotrif/Gilotrif (afatinib) have not been established in patients whose	NA	Approved	Approved ¹⁰⁰

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
	<p>tumours have L861Q, G719X, S768I, exon 20 insertions, and T790M mutations, which are also detected by the Therascreen EGFR RGQ PCR Kit.</p> <p>Specimens are processed using the QIAamp DSP DNA FFPE Tissue Kit for manual sample preparation and the Rotor-Gene Q MDx instrument for automated amplification and detection.⁸⁴</p>			
<p>Dako c-Kit pharmDx Gleevec/Glivec (imatinib mesylate)</p>	<p>The c-Kit pharmDx assay is a qualitative IHC kit system used on the Dako Autostainer for the identification of c-Kit protein/CD117 antigen (c-Kit protein) expression in normal and neoplastic FFPE tissues for histological evaluation. The c-Kit pharmDx rabbit polyclonal antibodies specifically detect the c-Kit protein in CD117 antigen-expressing cells.</p> <p>The c-Kit pharmDx is indicated as an aid in the differential diagnosis of GISTs. After diagnosis of GIST, results from c-Kit pharmDx may be used as an aid in identifying those patients eligible for treatment with Gleevec/Glivec (imatinib mesylate).</p> <p>Results from H&E stains and a panel of antibodies can aid in the differential diagnosis of GIST. Interpretation must be made by a qualified pathologist, within the context of a patient's clinical history, proper controls, and other diagnostic tests.⁸⁴</p>	<p>Approved Type: Test Kit Device Class: II First Issue Date: 2006-02-08 Licence Name: c-Kit pharmDx</p>	Approved ⁸⁴	Approved ¹⁰¹
<p>Inform HER2/neu Herceptin (trastuzumab)</p>	<p>The Inform HER2/neu gene detection system is a FISH DNA probe assay that determines the qualitative presence of HER2/neu gene amplification on FFPE human breast tissue as an aid to stratify breast cancer patients according to risk for recurrence or disease-related death. It is indicated for use as an adjunct to existing clinical and pathologic information currently used as prognostic indicators in the risk stratification of breast cancer in</p>	NA	Approved	Approved ¹⁰²

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
	patients who have had a priori invasive, localized breast carcinoma and who are lymph node-negative. ⁸⁴			
PathVysion HER-2 DNA Probe Kit Herceptin (trastuzumab)	The PathVysion HER-2 DNA Probe Kit (PathVysion Kit) is designed to detect amplification of the HER2/neu gene through FISH in FFPE human breast cancer tissue specimens. Results from the PathVysion Kit are intended for use as an adjunct to existing clinical and pathologic information currently used as prognostic factors in stage II, node-positive breast cancer patients. The PathVysion Kit is further indicated as an aid to predict disease-free and overall survival in patients with stage II, node-positive breast cancer treated with adjuvant CAF chemotherapy. The PathVysion Kit is indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered (see Herceptin package insert). ⁸⁴	Approved Type: Test Kit Device Class: III First Issue Date: 1999-03-26 Licence Name: PathVysion HER-2 DNA Probe Kit (LSI HER-2/neu SpectrumOrange/CEP 17 SpectrumGreen)	Approved	Approved ¹⁰³
PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Primary Antibody Herceptin (trastuzumab)	Ventana Medical Systems' PATHWAY Her-2 (clone CB11) is a rabbit monoclonal antibody intended for laboratory use for the semi-quantitative detection of c-erbB-2 antigen in sections of FFPE normal and neoplastic tissue on a Ventana automated IHC slide- staining device. It is indicated as an aid in the assessment of breast cancer patients for whom Herceptin treatment is being considered. ⁸⁴	Approved Type: Test Kit Device Class: II First Issue Date: 2006-12-27 Licence Name: PATHWAY Anti-HER-2/Neu Rabbit Monoclonal Primary Antibody Note: The antibody product available in Canada is produced from rabbit source rather than murine (mouse) source.	Approved	NA
SPoT-Light HER2 CISH Kit Herceptin (trastuzumab)	For IVD use. The SPoT-Light HER2 CISH Kit is intended to quantitatively determine <i>HER2</i> gene amplification in FFPE breast carcinoma tissue sections using CISH and bright-field microscopy. This test should be performed in a histopathology laboratory. The SPoT-Light HER2 CISH Kit is indicated as an aid in the assessment of	Approved Type: Test Kit Device Class: III First Issue Date: 2006-03-17 Licence Name: SPoT-Light HER2 CISH KIT	Approved	Approved ¹⁰⁴

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
	patients for whom Herceptin (trastuzumab) treatment is being considered. The assay results are intended for use as an adjunct to the clinicopathological information currently being used as part of the management of breast cancer patients. Interpretation of test results must be made by a qualified pathologist within the context of the patient's clinical history. ⁸⁴			
BOND Oracle HER2 IHC System Herceptin (trastuzumab)	The BOND Oracle HER2 IHC system is a semi-quantitative IHC assay to determine HER2 oncoprotein status in FFPE breast cancer tissue processed for histological evaluation following automated staining on the BOND-MAX slide-staining instrument. The BOND Oracle HER2 IHC system is indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered. ⁸⁴	NA	Approved	NA
HER2 CISH pharmDx Kit Herceptin (trastuzumab)	<p>HER2 CISH pharmDx Kit is intended for dual-colour chromogenic visualization of signals achieved with directly labelled in situ hybridization probes targeting the <i>HER2</i> gene and centromeric region of chromosome 17. The kit is designed to quantitatively determine <i>HER2</i> gene status in FFPE breast cancer tissue specimens. Red and blue chromogenic signals are generated on the same tissue section for evaluation under bright-field microscopy. The CISH procedure is automated using Dako Autostainer instruments.</p> <p>The HER2 CISH pharmDx Kit is indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered. Results from the HER2 CISH pharmDx Kit are intended for use as an adjunct to the clinicopathologic information currently used for estimating prognosis in stage II, node-positive breast cancer patients. This kit is for IVD use, only.⁸⁴</p>	<p>Approved</p> <p>Type: Test Kit</p> <p>Device Class: III</p> <p>First Issue Date: 2010-09-29</p> <p>Licence Name: HER2 CISH pharmDX Kit</p>	Approved	Approved ¹⁰¹

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
Inform HER2 Dual ISH DNA Probe Cocktail Herceptin (trastuzumab)	<p>The Inform HER2 Dual ISH DNA Probe Cocktail is intended for use in determining <i>HER2</i> gene status by enumeration of the ratio of the <i>HER2</i> gene to chromosome 17. The <i>HER2</i> and chromosome 17 probes are detected using two-colour CISH in FFPE human breast cancer tissue specimens following staining on Ventana BenchMark XT automated slide-stainers (using NexES software) by light microscopy. The Inform HER2 Dual ISH DNA Probe Cocktail is indicated as an aid in the assessment of patients for whom Herceptin (trastuzumab) treatment is being considered.</p> <p>This product should be interpreted by a qualified reader in conjunction with histological examination, relevant clinical information, and proper controls.</p> <p>This reagent is intended for IVD use.⁸⁴</p>	Approved Type: Test Kit Device Class: III First Issue Date: 2011-11-04 Licence Name: Inform HER2 Dual ISH DNA Probe Cocktail	Approved	Approved ¹⁰⁵
HercepTest Herceptin (trastuzumab); Perjeta (pertuzumab); Kadcyła (ado-trastuzumab emtansine)	<p>HercepTest is a semi-quantitative immunocytochemical assay to determine <i>HER2</i> protein over-expression in breast cancer tissues routinely processed for histological evaluation, and FFPE cancer tissue from patients with metastatic gastric or gastroesophageal junction adenocarcinoma. HercepTest is indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin (trastuzumab) treatment is being considered, and for breast cancer patients for whom Perjeta (pertuzumab) treatment or Kadcyła (ado-trastuzumab emtansine) treatment is being considered (see Herceptin, Perjeta, and Kadcyła package inserts).</p> <p>NOTE for breast cancer, only: All of the patients in the Herceptin clinical trials were selected using an investigational immunocytochemical CTA. None of the patients in those trials were selected using the HercepTest. The HercepTest was compared with the CTA on an independent</p>	Approved Type: System Device Class: II First Issue Date: 2013-09-26 Licence Name: Omnyx Image Analysis Application for Dako HercepTest	Approved	Approved 106,107

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
	<p>set of samples and found to provide acceptably concordant results. The actual correlation of the HercepTest to Herceptin clinical outcome has not been established.</p> <p>NOTE for gastric cancer, only: All of the patients in the phase 3 BO18255 (ToGA) study sponsored by Hoffmann-La Roche were selected using Dako HercepTest (IHC) and Dako HER2 FISH pharmDx Kit (FISH). However, enrolment in the BO18255 study was limited to patients whose tumours were HER2 protein overexpressing (IHC 3+) or gene-amplified (FISH+; HER2/CEN-17 ratio \geq 2.0). No patients were enrolled whose tumours were not gene-amplified, but HER2 protein was weakly to strongly overexpressing (FISH[-]/IHC 2+); therefore, it is unclear if patients whose tumours are not gene-amplified but are HER2 protein overexpressing (i.e., FISH[-], IHC 2+ or 3+) will benefit from Herceptin treatment. The study also demonstrated that gene amplification and protein over-expression (IHC) are not as correlated as with breast cancer; therefore, a single method should not be used to determine HER2 status.⁸⁴</p>			
<p>HER2 IQFISH pharmDx Kit Herceptin (trastuzumab); Perjeta(pertuzumab); Kadcyla (ado-trastuzumab emtansine)</p>	<p>HER2 IQFISH pharmDx is a direct FISH assay designed to quantitatively determine <i>HER2</i> gene amplification in FFPE breast cancer tissue specimens and FFPE specimens from patients with metastatic gastric or gastroesophageal junction adenocarcinoma.</p> <p>HER2 IQFISH pharmDx is indicated as an aid in the assessment of breast and gastric cancer patients for whom Herceptin (trastuzumab) treatment is being considered and for breast cancer patients for whom Perjeta (pertuzumab) or Kadcyla (ado-trastuzumab emtansine) treatment is being considered (see Herceptin, Perjeta, and Kadcyla package inserts).</p> <p>For breast cancer patients, results from the HER2 IQFISH pharmDx are intended for</p>	<p>Approved Type: Test Kit Device Class: III First Issue Date: 2004-08-30 Licence Name: HER2 IQFISH PharmDX Kit</p>	Approved	Approved ¹⁰⁷

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
	use as an adjunct to the clinicopathologic information currently used for estimating prognosis in stage II, node-positive breast cancer patients. ⁸⁴			
THxID-BRAF Kit Mekinist (trametinib); Tafinlar (dabrafenib)	The THxID-BRAF Kit is an IVD device intended for the qualitative detection of the BRAF V600E and V600K mutations in DNA samples extracted from FFPE human melanoma tissue. The THxID-BRAF kit is a real-time PCR test on the Applied Biosystems 7500 Fast Dx system and is intended to be used as an aid in selecting melanoma patients whose tumours carry the BRAF V600E mutation for treatment with dabrafenib (Tafinlar), and as an aid in selecting melanoma patients whose tumours carry the BRAF V600E or V600K mutation for treatment with trametinib (Mekinist). ⁸⁴	Approved Type: Test Kit Device Class: III First Issue Date: 2013-11-19 Licence Name: TxID-BRAF Kit	Approved	Approved ¹⁰⁸
cobas EGFR Mutation Test Tarceva (erlotinib)	The cobas EGFR Mutation Test is a real-time PCR test for the qualitative detection of exon 19 deletions and exon 21 (L858R) substitution mutations of the <i>EGFR</i> gene in DNA derived from FFPE human NSCLC tumour tissue. The test is intended to be used as an aid in selecting patients with metastatic NSCLC for whom Tarceva (erlotinib), an EGFR TKI, is indicated. ⁸⁴	Approved Type: Device Family Device Class: III First Issue Date: 2014-03-18 Licence Name: cobas 4800 System Assay Specific Analysis Package (ASAP) EGFR Mutation Test Kit	Approved	Approved ¹⁰⁹
Vysis ALK Break Apart FISH Probe Kit Xalkori (crizotinib)	The Vysis ALK Break Apart FISH Probe Kit is a qualitative test to detect rearrangements involving the <i>ALK</i> gene through FISH in FFPE NSCLC tissue specimens to aid in identifying patients eligible for treatment with Xalkori (crizotinib). This is for prescription use, only. ⁸⁴	Approved Type: Test Kit Device Class: III First Issue Date: 2012-03-14 Licence Name: Vysis ALK Break Apart FISH Probe Kit	Approved	Approved ¹¹⁰
cobas 4800 BRAF V600 Mutation Test Zelboraf (vemurafenib)	The cobas 4800 BRAF V600 Mutation Test is an IVD device intended for the qualitative detection of the BRAF V600E mutation in DNA extracted from FFPE human melanoma tissue. The cobas 4800 BRAF V600 Mutation Test is a real-time PCR test on the cobas 4800 system, and is intended to be used as an aid in selecting melanoma patients whose tumours carry the BRAF V600E mutation for treatment with vemurafenib. ⁸⁴	Approved Type: Test Kit Device Class: III First Issue Date: 2011-11-10 Licence Name: Cobas 4800 BRAF V600 Mutation Test	Approved	Approved ¹¹¹

Device Trade Name ⁸⁴ and Companion Drug	Indicated Use	Approval Status		
		Health Canada MDALL ⁹⁶	FDA ⁸⁴	CE-IVD Marked
Oncotype DX Breast Cancer Assay — Laboratory Diagnostic Test ¹¹²	This is a molecular diagnostic test used to inform the treatment (adjuvant chemotherapy in addition to hormone therapy) of patients with breast cancer by predicting chemotherapy benefit and likelihood of recurrence. ¹¹²	NA Note: The test is currently reimbursed publicly in Ontario, Quebec, and Saskatchewan, with a number of provinces considering public funding for qualified breast cancer patients. ¹¹³	Approved - CLIA — 05D1018 272	NA

ALK = anaplastic lymphoma kinase; CAF = cyclophosphamide, and 5-fluorouracil; CE = Conformité Européenne; CISH = chromogenic in situ hybridization; CLIA = Clinical Laboratory Improvement Amendment; CRC = colorectal cancer; CTA = clinical trial assay; EGFR = epidermal growth factor receptor; FFPE = formalin-fixed, paraffin-embedded; FISH = fluorescence in situ hybridization; GIST = gastrointestinal stromal tumour; H&E = hematoxylin and eosin; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemical; IVD = in vitro diagnostic; MDALL = Medical Devices Active Licence Listing; NA = not available; NSCLC = non-small cell lung cancer; PCR = polymerase chain reaction; TKI = tyrosine kinase inhibitor.

Appendix 3: Drug Reimbursement Processes By Canadian Federal, Provincial, and Territorial Public Drug Plans

Of note, the purpose of this summary is to briefly describe the information available in the public domain on the reimbursement processes by Canadian publicly funded drug programs. This appendix should be considered as an overview of the subject and does not represent a comprehensive or necessarily updated description of the drug reimbursement processes in Canada.

Federal Programs

Federal level drug plans in Canada are intended to provide coverage for eligible individuals (e.g., Non-Insured Health Benefits [NIHB] for First Nations and Inuit people). The drug formularies are updated regularly and include drugs based on the recommendation of the appropriate review board (i.e., the CDEC), along with other relevant considerations (including priorities and resources). The NIHB Drugs and Therapeutics Advisory Committee provides recommendations regarding formulary listings of drug products to the NIHB program.¹¹⁴

Provincial Programs

Alberta

For Alberta's Drug Benefit List, drugs are reviewed through the CADTH CDR. For drugs that are not reviewed by the CADTH CDR, the review is conducted by Alberta's Expert Committee on Drug Evaluation and Therapeutics, which then provides recommendations regarding the value and cost-effectiveness of the therapeutics to the Minister of Health. The final decision for inclusion in the Drug Benefit List is made by the Minister based on the recommendations of these boards, along with other considerations.¹¹⁵

In Alberta, cancer drugs (as specified in the Outpatient Cancer Drug Benefit Program) are provided to eligible residents (those who hold a valid certificate of registration under the *Health Insurance Premiums Act*, who are registered with the Alberta Cancer Registry, and who require cancer drugs to treat cancer) through Alberta Health Services.^{116,117}

British Columbia

In British Columbia, cancer treatment is covered through the British Columbia health care system, including surgery, chemotherapy, or radiation therapy. Additional prescription and medical costs (including non-cancer treatments and supportive care for cancer treatments) can be covered under a number of other options:¹¹⁸

- PharmaCare (which provides full or partial coverage for prescription drugs)
- Extended health plan coverage through private plans
- Ministry of Social Development & Social Innovation (those receiving income assistance will likely have prescriptions covered through PharmaCare Plan C)

- Palliative care benefits program (assists patients referred to the program with end-of-life care)
- Canadian Cancer Society (provides limited, short-term financial assistance for costs related to treatment)
- Special Authority, which grants full benefit status to a medication that would otherwise be considered by PharmaCare as a limited coverage drug.

In addition, the BC Cancer Agency will “reimburse, to the Communities Oncology Network hospital pharmacy, the actual acquisition cost of a Benefit Drug, up to the maximum price as determined by the BC Cancer Agency, based on the current brand and contract price.”¹¹⁹

New Brunswick

In New Brunswick, drugs eligible for New Brunswick residents through the New Brunswick Prescription Drug Program (NBPDP) are listed in the NBPDP Formulary. Most of the drugs included in the Formulary are reimbursed, with no criteria or pre-approval requirements; however, some drugs do require special authorization to be reimbursed. The NBPDP receives its listing recommendations from three drug review processes: the CADTH CDR, the pCODR, and the Atlantic Common Drug Review (ACDR).¹²⁰

Newfoundland and Labrador

In Newfoundland and Labrador, the Newfoundland and Labrador Prescription Drug Program is available for eligible individuals in the province and provides financial assistance for eligible prescription medications.¹²¹

In determining which pharmaceuticals to include in its coverage plan, Newfoundland and Labrador participate in the sharing of resources in reviewing submissions for coverage with ACDR, the CADTH CDR, and pCODR. Based on the final recommendations of these review bodies, a member from Newfoundland and Labrador provides a summary to the executive committee of the Department of Health and Community Services for review and final decision.¹²¹

Northwest Territories

In the Northwest Territories, all permanent residents are eligible for drug coverage.¹²² The Government of the Northwest Territories also sponsors the Extended Health Benefits program. This program provides Northwest Territories residents with certain benefits not covered by hospital and medical insurance, including 100% coverage for eligible prescriptions defined in the Health Canada NIHB drug benefits list, when prescribed by a health care professional and dispensed by a licensed pharmacist. If the prescribed drug is not included in the Health Canada NIHB drug benefits list, the health care professional or pharmacist may request prior authorization from Alberta Blue Cross on the patient’s behalf through this program.¹²³

Nova Scotia

In Nova Scotia, recommendations for the benefit status of drugs and devices are provided to the Department of Health and Wellness from either the Atlantic Expert Advisory Committee or CDEC. Given this recommendation, a drug may be added to the formulary as a full benefit, as an exception status drug (i.e., with criteria), or may be denied any benefit status.¹²⁴ The formulary advisory bodies include ACDR, the CDR, the Nova Scotia Drugs and Therapeutics Committee, and pCODR.¹²⁵ Additionally, the Drug Assistance for Cancer Patients program is a provincial program

that helps residents with cancer-related drugs and supplies indicated in the Nova Scotia Formulary. This program is available to individuals diagnosed with cancer who are permanent residents of Nova Scotia, with a gross family income of no greater than \$15,720 annually, and who do not have drug coverage (except Family Pharmacare).¹²⁶

Nunavut

Through the Department of Health, extended benefits are available to individuals enrolled with the Nunavut Health Care Plan who are non-beneficiaries 65 years of age or older, non-beneficiary Nunavut residents with a chronic disease or illness, or Nunavut residents who have used up or do not have other health care insurance options.¹²⁷

Ontario

In Ontario, decisions regarding the public funding of drug benefits are made by the Executive Officer of the Ministry of Health and Long-Term Care, Ontario Public Drug Programs (OPDP). These decisions are informed through the recommendations of an independent advisory, the Committee to Evaluate Drugs. Through the OPDP program, a drug may be provided through several public drug programs once it has been approved for funding.¹²⁸

Ontario has a number of programs related to cancer treatment. First, Ontario hospitals are reimbursed for the administration of injectable cancer drugs according to funding criteria, which is based on patient eligibility. These programs are administered by the Provincial Drug Reimbursement Programs Unit.¹²⁹ Through the New Drug Funding Program, the costs of newer (and often expensive) injectable cancer drugs, which have been evaluated and approved for coverage, are reimbursed to hospitals and cancer centres.¹³⁰ The Evidence-Building Program is a complement to the New Drug Funding Program. Through it, drugs with evolving evidence of benefits are funded for a limited basis to allow for the collection of real-world data, which can be used to inform the Ministry of Health and Long-Term Care of the clinical and cost-effectiveness of the product.¹³¹ Finally, the Case-by-Case Review Program is used in situations in which cancer patients are facing life-threatening circumstances and a satisfactory, publicly funded treatment option is unavailable to them. Requests to this program are available for cancer drugs that have been administered in hospitals, in outpatient or community use, or to provide continued treatment to patients who previously had been provided with the drug during a clinical trial or had it paid for by a third-party payer.¹³²

Prince Edward Island

Through Prince Edward Island (PEI) Pharmacare, there is a formulary of medications approved for coverage in PEI to residents who qualify for one of Health PEI's drug programs. The Pharmacare Formulary is compiled based on advice from the PEI Pharmacy Advisory Committee and on recommendations from one of the three drug review committees: ACDR or CDEC, or the Joint Oncology Drug Review Committee.¹³³ (Note: the latter is now pCODR.) Before new products, new dosage forms, new strengths, or new uses for existing products can be funded, they must be approved by the Minister of Health and Wellness. This decision is informed by the recommendations from CDEC, the Atlantic Expert Advisory Committee, or the pCODR Expert Review Committee.¹³⁴

In addition, Health PEI offers a High Cost Cancer Program, which subsidizes the cost of medications (approved by the program) for patients diagnosed with chronic myelogenous leukemia, advanced or metastatic breast cancer, renal cell carcinoma, or metastatic colorectal cancer.¹³⁵

Quebec

In Quebec, the decision of which drugs to list in the Public Prescription Drug Insurance Plan is determined by the Minister of Health and Social Services, in consultation with the Institut national d'excellence en santé et en services sociaux (INESSS).¹³⁶ Once a drug has been approved by Health Canada, the manufacturer wishing to have his or her drug product reimbursed by the provincial drug plan must submit an application to register a project with INESSS. After the complete application has been received, INESSS will begin an evaluation. There are several evaluation criteria: first and foremost is the therapeutic value of the drug, as well as the reasonableness of price, cost-effectiveness ratio, the impact on the health of the population and on the health care system, and the advisability of adding the product to the list for coverage in the prescription drug insurance plan. Once the evaluation has been completed, the committee can provide one of the following recommendations: registration without restriction, registration as an exceptional medication, registration under the traditional subsection or the subsection with follow-up, refuse the listing, or file it under study. These recommendations are then taken into account by the Minister in decisions of whether to add a medication to the list.¹³⁷

Cancer medications used by hospitals or cancer centres are funded by the province of Quebec, which is the primary payer for cancer medications. These medications are funded through hospital drug budgets (with each hospital having its own formulary for which medications can be used at that particular institution) and the provincial drug benefits plan (which covers medications that are taken at home and not paid for by the hospital).¹³⁸

Saskatchewan

In Saskatchewan, the Drug Advisory Committee of Saskatchewan (DACS) — an appointed committee of public representatives and clinical specialists — evaluates and advises the Minister of Health of which drugs should be included in the Saskatchewan Formulary, Saskatchewan Cancer Agency Drug Formulary, and Hospital Benefit Drug List. The provincial drug formulary is updated annually, and drug coverage decisions are based on a number of factors including the recommendations of CDEC, as well as provincial priorities and resources.¹³⁹

Approved cancer drugs (including those administered by injection or taken orally at home) are paid for by the Saskatchewan Cancer Agency (through funding from the Government of Saskatchewan). The decision of which drugs to approve and fund is the responsibility of the Agency. As noted on its website,¹⁴⁰ “The Cancer Agency’s Pharmacy and Therapeutics Committee will prepare submissions to DACS requesting new cancer drug funding and revisions to the formulary based on the scientific evidence of safety, how effective the drug is, and impact on patient treatments. Provincially, DACS will make recommendations to the Ministry of Health on all drug approvals, including cancer drugs.” This decision involves comparing the medical benefit of cancer drugs with the overall cost.¹⁴⁰