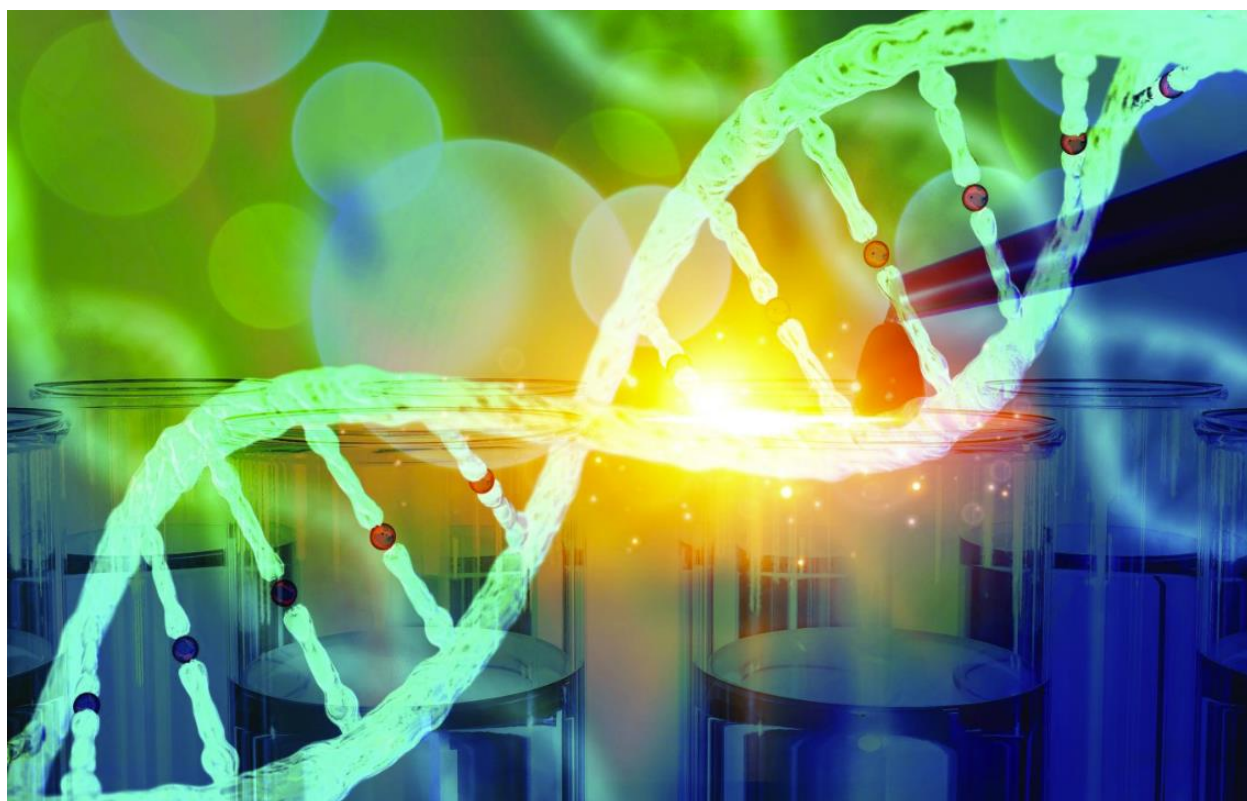


# A REVIEW OF PRECISION MEDICINE COMPANION DIAGNOSTICS IN CANADA

## ARE WE THERE YET?



CANADIAN CANCER  
SURVIVOR NETWORK  RÉSEAU CANADIEN DES  
SURVIVANTS DU CANCER

November 2020

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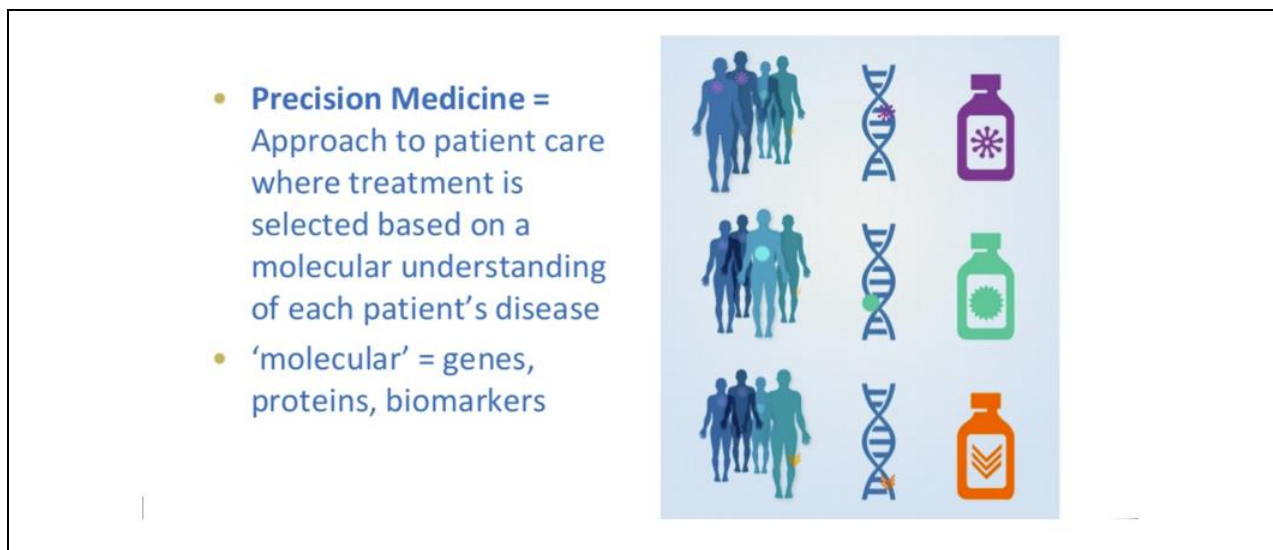
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## PART I: INTRODUCTION

The **Canadian Cancer Survivor Network (CCSN)** is a Canadian-led charity that provides support for cancer patients, survivors and caregivers. CCSN was created by a group of Canadians concerned about cancer and cancer survivorship issues and is committed to improving the lives of Canadians touched by cancer. As part of its vision to ensure patients gain access to knowledge on cancer treatments, options and outcomes so they can end disparities in patient care and treatment across the country, CCSN commissioned a review of precision medicine companion diagnostic testing in Canada through a literature review and a series of stakeholder interviews. They wished to determine if there were any challenges or barriers that would ultimately impact patient access and then issue a series of recommendations to help inform thoughtful change to address those concerns. The review began on June 24, 2020 and ended on August 24, 2020. The following report is the result of the literature review, stakeholder interviews and patient interviews that ensued.

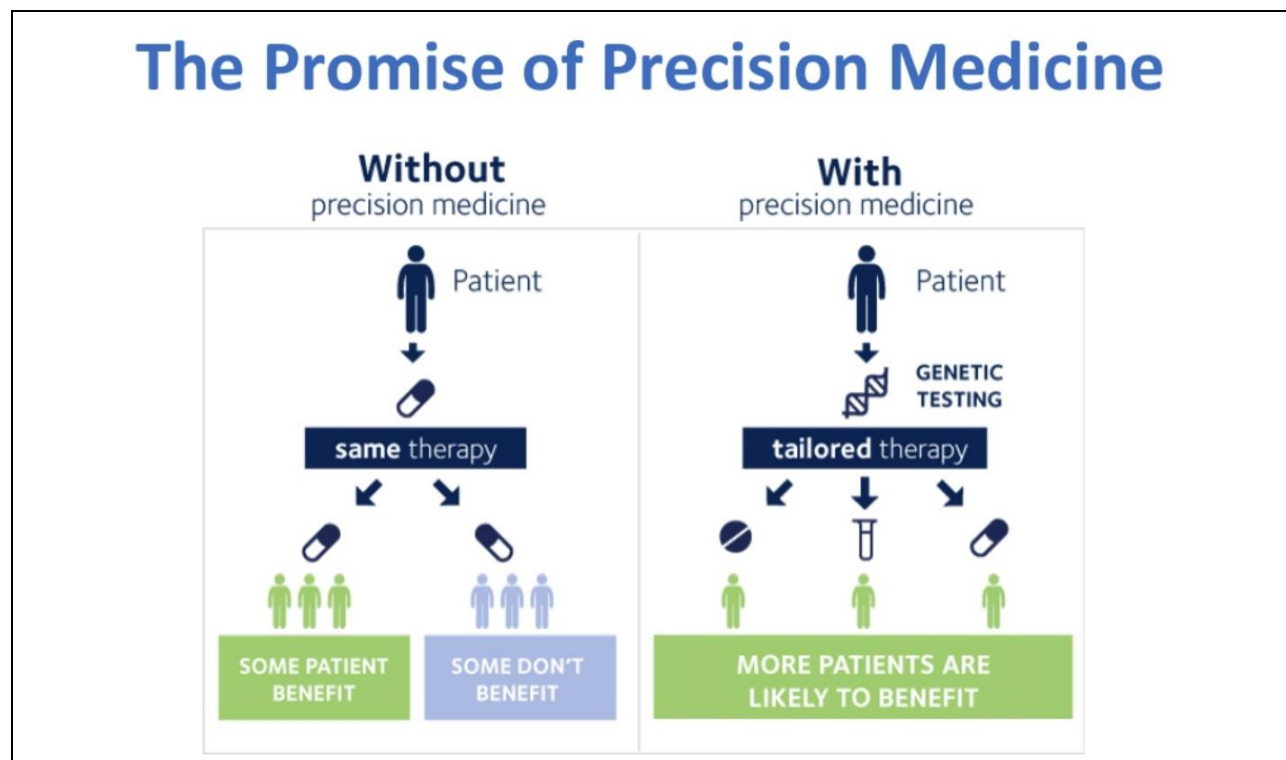
The rise of precision medicine in Canada has generated a desire to have reliable and accurate methods of identifying patients who will benefit from oncology drug therapies in clinical practice. While the term “precision medicine” is often used interchangeably with “personalized medicine,” it is important to note the latter implies the therapy is specific for each individual patient. Precision medicine is directed at delivering the right drug to the right patient at the right time, promising more efficient use of the healthcare resources by targeting those patients most likely to respond to the therapy. Precision medicines can identify biological information (genes, RNA/DNA, or proteins) to stratify patients, targeting those patients most likely to respond to a specific treatment. In precision medicine, diagnosis and treatment are intrinsically linked. While this field has evolved using different names (personalized medicine, targeted treatment, individualized care, etc.), for the purposes of this report, the current preferred term is “**precision medicine.**”



**Figure 1: Precision Medicine in the Treatment of Cancer**

Currently, clinicians prescribing cancer drug therapies have departed from the age of one-size-fits-all drugs to the age of precision therapeutics, characterized by higher rates of effective therapies and lower rates of adverse events. Previously, the anti-cancer therapy drugs prescribed typically depended upon the type of cancer, size, and stage, along with patient preferences. With precision medicine, information

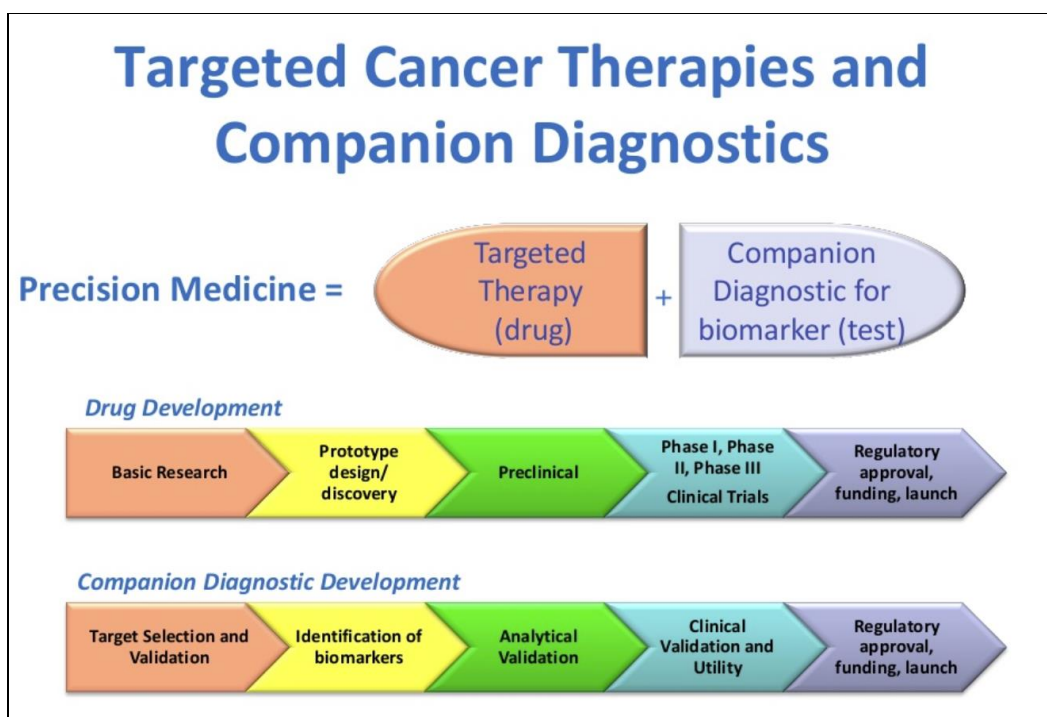
about genetic changes in the tumour is used to determine the best management strategy for each patient. Although there is still a great deal to learn, the hope is that precision medicine will result in cancer patients achieving both better treatment outcomes and fewer side effects.



**Figure 2: The Promise of Precision Medicine**

Identifying precisely who will benefit from a given anti-cancer treatment and which patients should not receive a therapy because of an increased risk of side effects, begins with the identification and validation of a biomarker. Biomarkers can “*reveal biological processes, pathogenic process, or a pharmacologic response to a therapeutic intervention.*”<sup>1</sup> “*The pace of biomarker discovery has increased exponentially over the last few years and this has ushered in the era of precision medicine, with a growing arsenal of treatments tailored to specific cancer patient populations.*”<sup>2</sup> “*The success of biomarker-based treatments, however, lies in the accurate identification of patients exhibiting required biomarker expression.*”<sup>2</sup> To identify those cancer patients who are candidates for precision medicines, clinicians rely upon assays or tests known as **companion diagnostics**.

“*When more patients who are appropriate for treatment are identified, more patients will receive the appropriate treatment.*”<sup>2</sup> The companion diagnostic test is the key to not only identifying the right patient population, but also to reaching as many patients as possible within that population.



**Figure 3: Precision Medicine – Targeted Therapy and its Associated Companion Diagnostic**

Companion diagnostics are so named because these assays or tests are specifically developed for use as a companion to a particular drug therapy. In addition to identifying the correct patient population, companion diagnostics may also help avoid adverse drug reactions by allowing clinicians to identify patients who are at increased risk for serious side effects from certain therapies. Our understanding of oncology and response to therapies has evolved over the years due to a better understanding of the molecular drivers of disease. Subsequently, the treatments that target these processes have shown improved health outcomes, most notably, with extensions in overall survival. These benefits are extremely important to cancer patients and their families.

Several clinical studies and data from clinical registries have clearly demonstrated a difference in how patients respond to the same drug therapy. As many *“as 75% of cancer patients fail to respond favorably to the same prescribed cancer drug.”*<sup>3</sup> Companion diagnostic tests can provide information that is essential for the safe and effective use of a corresponding drug or biological product. These tests can certainly spare patients from unnecessary treatment-induced toxicities and immediate disease progression if they do not qualify for the drug therapy based on their cancer’s molecular/genetic characteristics.

This review has been undertaken by the Canadian Cancer Survivor Network as part of an awareness campaign about the state of companion diagnostics in Canada. This white paper will provide an overview of the current use of companion diagnostic tests for the prescription of precision cancer drug therapies throughout Canada, identifying gaps and challenges related to the approval, evaluation, funding, adoption, access, and implementation in health systems. While not exhaustive, a robust literature review was conducted on behalf of CCSN to identify key articles about the gaps and challenges presented in this paper as well as proposed recommendations to help foster a homogeneous health system surrounding access to companion diagnostic testing for patients in Canada. In addition, stakeholders were interviewed for the purposes of capturing their valuable perspectives on the use of

companion diagnostic testing in Canada. Their perspectives were incorporated throughout the paper to help inform and guide recommendations.

## PART II: DEFINING COMPANION DIAGNOSTICS IN THE CANADIAN LANDSCAPE

Companion diagnostics are an approved method to clinically identify subpopulations of cancer patients, allowing for more individualized drug treatments based on a specific patient's likelihood of response.

The era of companion diagnostics started in 1998 with the FDA approval of Herceptin, the breast cancer drug that shuts off a protein (HER-2) present in abnormally high amounts in approximately one quarter to one third of breast cancer patients. Patients diagnosed with HER 2-positive breast cancer are typically diagnosed with aggressive disease. The companion diagnostic test identifies overexpression of HER2 or extra copies of the HER2 gene in the patient's tumour, indicating that Herceptin could be an effective therapy for the management of that patient's breast cancer. Thus, the era of companion diagnostics erupted.

Essentially, companion diagnostics allow for the safe and effective use of a corresponding drug or biological product. In general, for cancer treatment, companion diagnostics are designed to pair up a targeted agent with a patient whose cancer harbours the defined molecular characteristics upon which the drug acts. A mutant protein provides one example that can be targeted this way by a combined drug and diagnostic. *"Treatment with Vemurafenib, a V600E mutant BRAF kinase inhibitor used in melanoma, needs a patient to be confirmed as V600E mutation positive by a companion diagnostic."*<sup>4</sup> Patients who do not harbor this mutation should therefore not be treated with Vemurafenib.

In April 2020, the United States Food & Drug Administration (FDA) issued a final Guidance Document for industry, describing considerations for the development and labelling of companion diagnostic devices to support the indicated uses of multiple drug or biological oncology products. The document issued a definition for a companion diagnostic as an *"...in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product...It aims to match therapeutic products to those patients (and only those patients) who will positively respond to that therapeutic product, to maximize benefits and minimize risks from the therapeutic products received."*<sup>5</sup> It went on to highlight the role of precision oncology and what precision oncology depends on:

- 1) "Understanding the molecular pathophysiology of cancer and
- 2) "The ability of companion diagnostics to accurately and reliably detect and measure molecular biomarkers. These companion diagnostics inform both the development and the approved use of therapeutic products."<sup>5</sup>

In Canada, the definition is not quite as straightforward. The Canadian Agency for Drugs and Technologies in Health (CADTH) issued an environmental scan in June 2016 on *Pharmaceuticals Requiring Companion Diagnostics*, which contained a definition of companion diagnostics: *"tests used to measure an individual's protein or gene expression, or detect genetic variation (biomarkers)."*<sup>6</sup> The use of biomarkers to determine individual response to drug therapy is commonly referred to as pharmacogenomics where companion diagnostics have the potential to guide the choice and/or dose of a drug therapy to improve patient outcomes. CADTH also issued a definition in its 2019 *Appendix-specific Guidance Document for Treatments with Companion Diagnostics* (consistent with its previously issued definition): *"A test that measures an individual's protein or gene expression or detects genetic variation for the purpose of informing a treatment decision."*<sup>7</sup>



Of noteworthy importance is the fact that companion diagnostics may be considered as:

- In vitro diagnostic devices (IVDDs): kits manufactured, validated and sold by diagnostic companies.
- Laboratory developed tests (LDT): tests developed and validated at the local laboratory level.

In Canada, a definition that incorporates or considers both IVDD kits and LDTs is less than ideal. From a regulatory perspective, a companion diagnostic developed from a diagnostic company is considered an IVDD and is regulated through the Medical Device Bureau of the Therapeutic Products Directorate (TPD) at Health Canada, while a drug product is regulated by the TPD or the Biologics and Genetics Therapies Directorate (BGTD).

Oncology drugs, IVDDs and LDTs enter the healthcare system through different pathways with little, if any, formal coordination between them. As the BioCanRx Paper has appropriately highlighted in their June 2017 publication, this lack of formal coordination between drugs, IVDD and LDTs presents a challenge to the current organization of the healthcare system, as decisions on which drugs, medical devices and laboratory tests to provide for patients are made by different decision-makers.<sup>8</sup> This can create a great deal of inconsistency and a heterogeneous landscape throughout Canada for patients accessing companion diagnostics. Consequently, patients may have their treatment options and outcomes impacted. *“Equitable patient access across the country should be an objective of companion diagnostics policy in Canada. However, the decentralized nature of healthcare system decision-making throughout the country, along with limited budgets and resources for adopting healthcare innovations collectively challenge this objective.”*<sup>8</sup>

Most companion diagnostics in use throughout Canada are LDTs or lab developed tests. These tests do not undergo any regulatory approval process at Health Canada as they are developed and validated at the local lab level. When interviewing stakeholders, a distinction was made between the two types of companion diagnostics in Canada at the onset of their interview. Some stakeholders were well acquainted with the differences between the two types of companion diagnostics, while others were not. Often the two can be mistaken for each other.

The following stakeholders were interviewed and contributed meaningful and thoughtful input when capturing the challenges and barriers related to the clinical implementation and access to companion diagnostics in Canada:

STAKEHOLDER INTERVIEWS	
<b>Robin McGee, PhD</b> (Patient Perspective)	Stage IV Rectal Cancer Patient, Psychologist, Halifax, Nova Scotia (July 7, 2020)
<b>Dr. Judith Glennie</b> (CAPT)	President of J. L. Glennie Consulting Inc., Toronto, Ontario (July 8, 2020)
<b>Dr. Calvin Law</b> (Oncology) (Clinician)	Chief Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Ontario (July 16, 2020)
<b>Sylvie Bouchard</b> (HTA)	INESSS, Montreal, QC (July 22, 2020)
<b>Brandon Levac</b> (Pharma)	Bayer, Toronto, Ontario (July 24, 2020)
<b>Jill Hamer-Wilson</b> (CCTG)	Lung Cancer Patient Rep, Ottawa, Ontario (August 6, 2020)
<b>Dr. Aaron Pollett</b> (Pathologist – LDT)	Provincial Head, Pathology & Laboratory Medicine, Cancer Care Ontario; Mt. Sinai Hospital, Toronto, Ontario (August 12, 2020)

<b>WRITTEN REPLIES PROVIDED BY:</b>	
<b>Trevor Richter, CADTH (HTA)</b>	Director, Pharmaceutical Reviews, CADTH (August 5, 2020)

*(Please note: Each stakeholder interviewed by the author was furnished with a list of questions to which they provided insightful and meaningful input. Please see **Appendix A** for the list of stakeholder interview questions. As the stakeholder interviews evolved and the literature review was completed, a more informed interview process took place. Hence, some of the interview questions became irrelevant for the Canadian setting; specifically, the interview question about co-development of the companion diagnostic and its associated drug.)*

The Canadian Agency for Drugs and Technologies in Health (CADTH) could not accommodate a telephone interview but was kind enough to furnish written replies to interview questions, **Trevor Richter**, Director of Pharmaceutical Reviews at CADTH, provided the following current definition for companion diagnostics:

*“Companion diagnostics are **laboratory tests** that provide information essential for the safe and effective use of particular therapeutic drugs. They work by detecting specific biomarkers that predict more favourable responses to certain drugs. In practice, companion diagnostics can identify patients who are likely to benefit or experience harms from particular therapies or monitor clinical responses to optimally guide treatment adjustments.”*

### PART III: IDENTIFYING THE BARRIERS & CHALLENGES IN THE CANADIAN LANDSCAPE

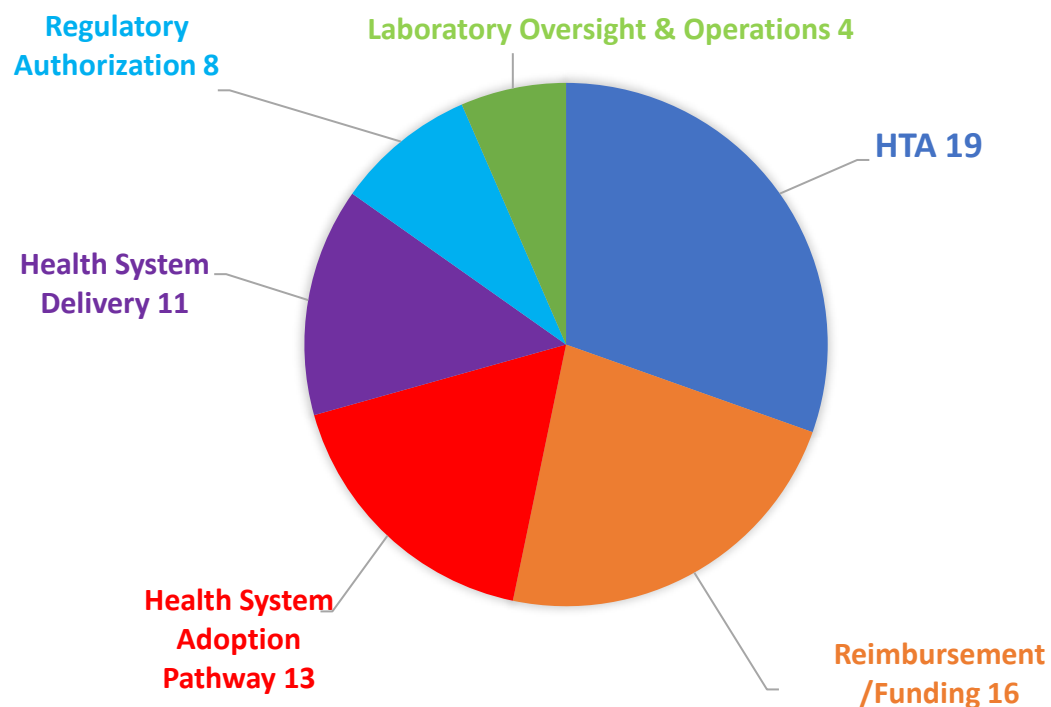
The author conducted a literature review on behalf of CCSN to identify the key challenges and barriers related to the clinical implementation of and patient access to companion diagnostics within the Canadian healthcare system. The articles reviewed were published between June 2010 and June 2020. 39 articles were selected containing relevant content on companion diagnostic testing. 22 articles were directly cited for the purposes of this report because they contained relevant stakeholder views about or issues related to the implementation of and access to companion diagnostic testing in Canada. Specifically, the articles cited related to one or more of the following categories:

- A. Health Technology Assessment (HTA).
- B. Reimbursement/Funding.
- C. Health System Adoption Pathway.
- D. Health System Delivery.
- E. Regulatory Authorization.
- F. Laboratory Oversight & Operations.

The categories representing the various issues identified most frequently in the 22 selected articles are shown in the figure that appears below (**FIGURE 4**).

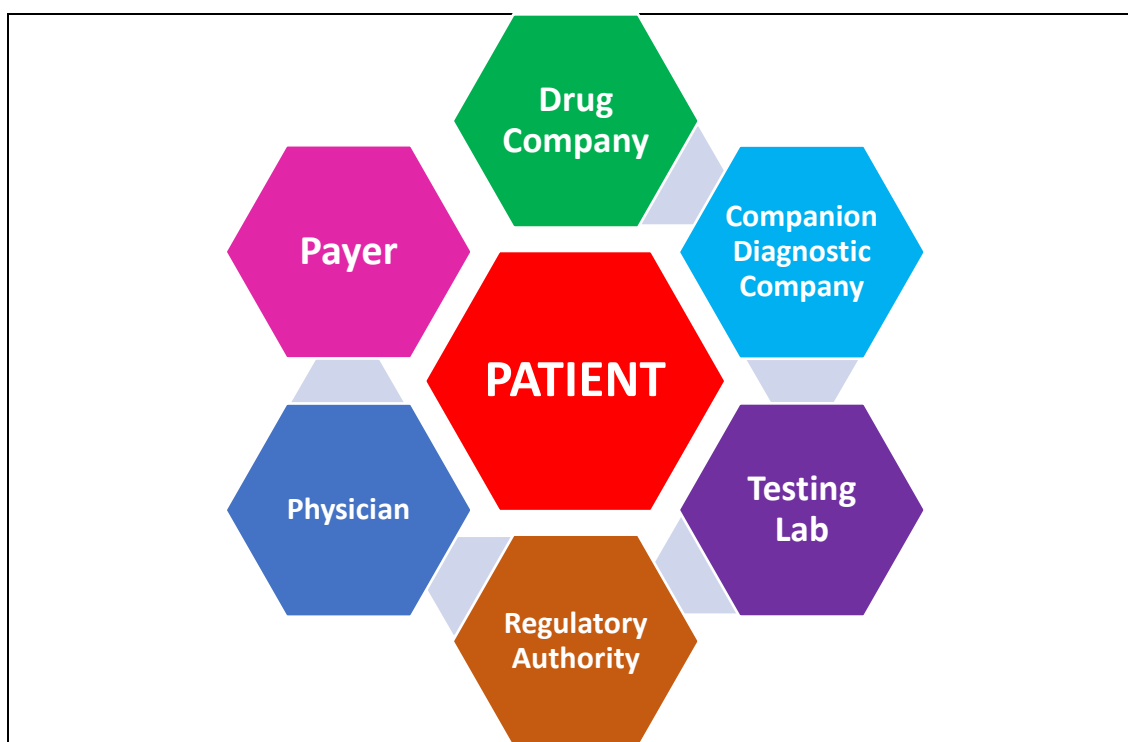


**FIGURE 4: ISSUES IDENTIFIED IN THE LITERATURE**



Each category identified various stakeholder issues which are discussed below, followed by recommendations appearing in PART V of this report to support a comprehensive and all-inclusive approach to the delivery of and patient access to companion diagnostics.

The articles reviewed in the literature identified several stakeholders who hold very different perspectives on the value of the companion diagnostic (See Figure 5 below).



**Figure 5: Stakeholders Most Readily Identified in the Literature**

Different stakeholders may perceive different value propositions of the therapeutic agent versus the companion diagnostic. The patient, however, was typically at the centre of their shared common interests. Clearly, the value to the patient who requires the companion diagnostic for clinical information to help them better manage their disease is not financially motivated. But, as the results of the stakeholder interviews clearly demonstrate, every stakeholder has the best interests of patients in mind as they navigate the companion diagnostic landscape. When asked *“Who would you consider to be the various stakeholders impacted both negatively and positively from the implementation or lack of implementation of companion diagnostics in Canada?”* all interviewed stakeholders provided *“Patients”* as their first reply.

#### **A. HEALTH TECHNOLOGY ASSESSMENT (HTA)**

Issues related to Health Technology Assessment (HTA) were most frequently cited in the literature. The October 2017 IHE/CAPT Paper<sup>9</sup> and BioCanRx Paper<sup>8</sup> nicely captured these issues through an extensive literature review. Additional articles underscored and echoed the challenges identified as follows:

Once Health Canada has approved a cancer drug for use in Canada, the country's provinces and territories must decide if the drug will be eligible for public reimbursement. The CADTH pan-Canadian Oncology Drug Review (pCODR) plays an important role in their decision-making processes. Through the pCODR process, CADTH conducts thorough and objective evaluations of clinical, economic, and patient evidence on cancer drugs, and uses this evaluation to provide reimbursement recommendations and advice to provincial and territorial public drug plans (with the exception of Quebec, where the Institut national d'excellence en santé et en services sociaux (INESSS) is responsible for HTA) and

provincial cancer agencies. Reimbursement recommendations are made by CADTH's pCODR Expert Review Committee (pERC) comprised of:

- Medical oncologists.
- Physicians.
- Pharmacists.
- Economists.
- An ethicist.
- Patient members.

The drug plans and cancer agencies make their final reimbursement and coverage decisions based on pERC's funding recommendations and other factors, such as their program mandates, jurisdictional priorities, and budget impact.<sup>10</sup>

If an oncology drug has a related companion diagnostic, then the manufacturer should provide specific clinical information and pharmacoeconomic information related to the companion diagnostic, if Health Canada requires biomarker testing to guide patient treatment. CADTH will investigate those factors relevant to biomarker testing that would inform the implementation of the associated drug under review. While CADTH will receive additional input in its review of companion diagnostics, there is no formal process for the evaluation of companion diagnostics in Canada. Currently, HTAs are used to inform reimbursement recommendations for companion diagnostics, but in addition to CADTH, the HTA may come from a variety of sources: provincial HTA agencies (e.g. INESSS, OHTAC), provincial ministries of health, and hospitals. Once a recommendation has been made, funding for a companion diagnostic may come from different sources, including hospitals, provincial cancer agencies, pharmaceutical companies and private payers.



**Figure 6: Understanding Precision Medicine in Cancer Treatment – Provincial Funding of Companion Diagnostics**

In September 2019, CADTH issued *Guidelines for the Economic Evaluation of Health Technologies in Canada – a specific guidance for treatments with companion diagnostics*.<sup>7</sup> The intent of this document was to provide additional guidance that pertains specifically to the economic evaluation when assessing the treatment and its associated companion diagnostic. To the author's knowledge, these guidelines

have not been applied. The author of the BioCanRx Paper, Katherine Bonter, summarized the HTA issues as *“disjointed coverage decisions, a non-transparent evaluation process; lack of clarity in how decision-makers prioritize tests for evaluation; and hospital-and Health Technology Assessment (HTA)-based decisions which differ within each province.”*<sup>8</sup> Katherine Bonter also highlighted the interprovincial variability in regulations and operations and data requirement as issues that affect companion diagnostics uptake and deter development. Regulation of diagnostic services is at the provincial level, which can lead to different regulatory frameworks and approaches. In addition, the process to gain access to diagnostic tests and operations of diagnostic labs can vary dramatically across the provinces. Finally, although data to support the value and utility of companion diagnostics is important, criteria used may be ill-defined and payers put the onus on manufacturers to bear the costs of data and analytics.

Concerns were expressed regarding cross-jurisdictional inconsistency in the processes to approve, fund and access diagnostic tests. There are interprovincial differences in HTA efforts and initiatives which may cause inequitable implementation and patient access to diagnostic tests. This in turn could result in different standards and criteria producing *“considerable duplication of effort”*<sup>6</sup> across the country.

**Brandon Levac** from Bayer Canada provided thoughtful input when asked if standardized methods for determining reimbursement for diagnostic tests were lacking in Canada: *“...Yes, definitely not just methods but the process by province is unclear with limited transparency throughout.”* He went on to say: *“For new, non-proprietary diagnostics, it would be good if standards are established on the HTA/funder side for validation and determination of clinical utility; it would be fair for drug manufacturers to support the research in establishing this with the pathology labs, and perhaps in doing so, providing interim funding for the testing. Following this, there should be a transparent process towards funding of the diagnostics.”* When asked if there were any solution in helping to address the challenges related to implementing or accessing the challenges related to companion diagnostics, Mr. Levac provided the following reply: *“As a step after individual provincial processes are improved, public funders should consider establishing a pan-provincial diagnostic testing strategy and representative organization; this would allow for 1) uniform testing across jurisdictions; 2) easier industry-public partnering, especially if longer-term utility research is required; 3) standardization of testing, and consolidation of purchasing for efficiencies (e.g. capital equipment, reagents, etc.).”*

The lack of standardized methods for reimbursement of companion diagnostics was identified by other interviewed stakeholders and was underscored in the literature. **Dr. Robin McGee**, well known psychologist and stage IV rectal cancer patient in Halifax, Nova Scotia, spoke to the lack of standardization in the quality assurance of the diagnostic tests she believes are performed in different laboratories across Canada. She also spoke to the challenges and struggles she has been experiencing since her original stage III diagnosis ten years ago, which ultimately progressed to stage IV disease, requiring access to companion diagnostics and, more recently, Next Generation Sequencing (NGS) testing: *“There is a lack of consistent HTA process and mechanism to properly and thoroughly address new evidence overseeing diagnostic tests. There is tremendous inconsistency across the country with our counterparts. Having had to access treatments in various provinces, I am well acquainted. Some provinces are more on the ball...than others. BC and Ontario are not experiencing the same challenges as Nova Scotia. There should be a widespread reimbursement approval process for these diagnostic tests throughout the various provincial jurisdictions.”*

**Dr. Calvin Law**, Chief of the Odette Cancer Centre at the Sunnybrook Health Sciences Centre in Toronto, Ontario, maintained that there is *“too much inconsistency from province to province and essentially it’s the postal code that dictates what therapy a patient receives. We should be standardizing these*

*companion diagnostic tests for the benefit of patients who stand to receive and benefit from the associated therapies. And there should be a concerted national plan for this. All stakeholders should come together to bring this plan to light.”*

**Sylvie Bouchard**, Director of INESSS, spoke about the HTA process Quebec has in place for the review of companion diagnostic tests. *“As of three years now, there is a written process in place at INESSS for drug manufacturers to pursue if they wish to have their drugs reviewed with their associated companion diagnostics. And it’s noted at the pre-NOC level – the manufacturer has to advise us that in two months it will send off a submission for a specific drug and its companion diagnostic. The assessment is performed at the same time by INESSS. The assessment of the companion diagnostic is included in the report of the drug assessment. We believe we are pioneers in the co-assessment of the drug and its associated companion diagnostic. Review of the diagnostic and its associated drug will ensure that the recommendation to the minister will not delay access to patients who require the test. It will permit timely access to the diagnostic test and determine patient candidacy to therapies that could improve outcomes for those patients who are identified.”*

## **B. REIMBURSEMENT/FUNDING**

Once an oncology drug has been authorized for sale through a Health Canada review, it will be reviewed by CADTH’s pCODR process, or INESSS in Quebec, both of which assess the drug by reviewing scientific evidence on its comparative clinical and cost effectiveness. Funding recommendations are then issued to inform a reimbursement decision at the provincial jurisdictional level. Specific reimbursement policies for companion drugs and associated diagnostics have not been identified from any of the provincial bodies except for INESSS. In addition to these publicly funded drug plans, private insurance is also available in Canada to assist with costs related to the drugs.

In the absence of a comprehensive and standard HTA process that includes the oncology drug and companion diagnostic test in Canada (INESSS notwithstanding), provincial and territorial jurisdictions may decide to reimburse a particular oncology drug without its associated companion diagnostic. The ministries of health rely on the funding recommendations issued by HTA expert committees who take the time and effort to diligently review these drugs.

The issuing of a positive funding recommendation after an HTA review is certainly fraught with challenges, according to the stakeholders interviewed and the literature reviewed. Following a positive HTA recommendation, funding for the oncology drug comes from a different budget than the funding of the companion diagnostic. *“Within health system or healthcare institution budgets, funding is allocated for drugs separately from funding allocated for laboratory services (testing). Consequently, the very element that makes companion diagnostic tests so unique and useful – the pairing of a diagnostic test with a drug – challenges siloed healthcare budgets.”*<sup>8</sup> Hence, there are two separate budgets in place: a drug budget and the laboratory services budget – either in the ministry of health budget or that of a healthcare institution (i.e. hospital). The diagnostic testing, funding and decision-making authority typically resides with institutional laboratory services, budgets and controllers, while oncology drugs are primarily funded by provincial pharmaceutical budgets. Most stakeholders identified a disconnect between the drug approval and the funding of its companion diagnostic.

Funding decisions for companion diagnostic tests are made at the provincial level and decisions may vary across jurisdictions. This creates inequity and inconsistent access for patients across Canada. Some provinces may not have dedicated processes in place to review, fund, and implement such tests, which

may result in increased pressure on individual hospitals. Hospital-based decisions may also result in considerable duplication of effort and prevent standardization of policies across institutions. Another consequence resulting from a lack of jurisdictional funding is the inappropriate coverage assumed by the drug manufacturer for the companion diagnostic, hoping for increased patient access and a return on investment.

**Dr. Judith Glennie**, President of J.L. Glennie Consulting Inc. and Past President of the Canadian Association for Population Therapeutics (CAPT), commented on the reimbursement challenges associated with companion diagnostics in Canada, in part resulting from HTA challenges – that is, no link between drug approvals and companion diagnostic funding. *“Overall, the cost of the companion diagnostic test is relatively small when compared to the typical cost of the associated therapy. The therapy costs hundreds of thousands of dollars. The diagnostic, however, costs hundreds of dollars. The challenge becomes being able to introduce the diagnostic into the healthcare system with the therapy where patients can easily access the test to identify as suitable for treatment and ensure optimal outcomes. There is a lab operations challenge, due to an alignment of resources and budgetary restrictions resulting from siloed budgets. There are currently no standardized frameworks overseeing funding, which are definitely required.”*

In addition, as identified in the literature,<sup>11</sup> the price of the companion diagnostic test may not be included in the overall cost-effectiveness ratio calculation. It has been demonstrated that the drug manufacturer of the associated therapeutic may often pay for the companion diagnostic test. Subsidizing the implementation and provision of the companion diagnostic test should not be the responsibility of the pharmaceutical manufacturer. This is neither a sustainable solution for the manufacturer nor the healthcare system. All stakeholders have an interest in ensuring the right patient receives the right therapy at the right time. Reimbursement and access to diagnostic testing should remain in the hands of the healthcare system overseeing care of their patient populations. The lines should never be blurred or compromised as to who oversees and provides care to these oncology patients or other patient populations.

**Brandon Levac** from Bayer commented on the funding of companion diagnostics in the public health care system. *“In terms of barriers to reimbursement of the companion diagnostic: not coordinating drug access with test access, reimbursement of the test ties with public drug coverage, which can be a disadvantage for patients with private drug coverage that is more comprehensive, and the expectation that drug manufacturers fund the test.”*

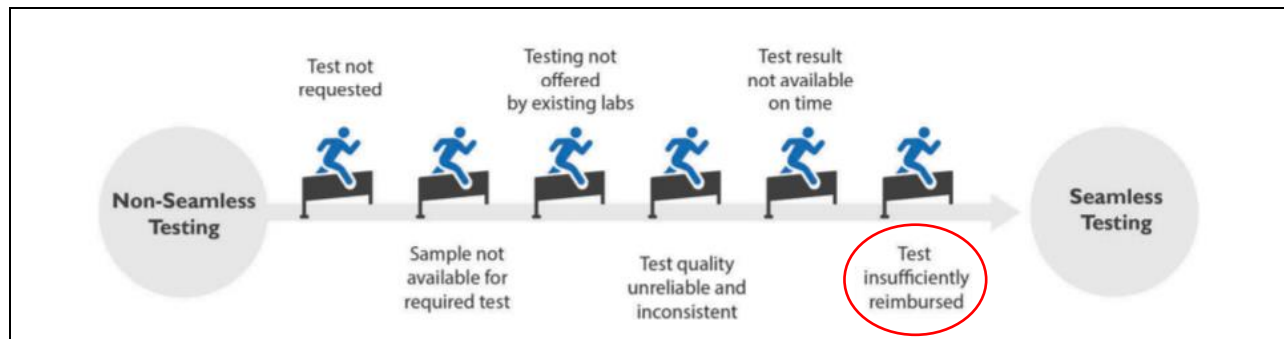
He went on to say: *“Companion diagnostic testing is a public expenditure, it is part of the healthcare infrastructure – it is not always appropriate for drug manufacturers to pay for this, especially in the long term. Also, it is not a long-term solution since the typical market exclusivity period for a drug is only approximately eight years. Test costs can vary significantly between provinces and labs – they are not uniform across Canada and are not within the control of a drug manufacturer (versus the drug itself).”*

The Ontario Personalized Medicine Network reinforced this point in their Subcommittee Report: *“...the cost of the companion diagnostic may not be included in the overall cost-effectiveness ratio calculation. For example, the industry provider of the associated therapeutic often pays for (or is forced to cover the cost of) the companion diagnostic. This complicates the HTA process.”<sup>11</sup>*

An online paper published in April 2020<sup>12</sup> identified implementation challenges facing companion diagnostic tests and delaying clinical uptake. Six were identified (See Figure 7 appearing below): “*Test Insufficiently reimbursed*” was highlighted and was determined to be the key to driving test adoption by



labs and physicians. Business behaviors supporting testing must be viable to sustain testing. Otherwise, testing will be suboptimal.<sup>12</sup>



**Figure 7: Six Common Barriers to the Adoption of Companion Diagnostic Tests**

Many laboratories within Canada cannot afford or are not technologically equipped to perform commercially developed companion diagnostic tests approved by regulatory authorities (for example, Health Canada approved in vitro diagnostic device [IVDD] kits). Consequently, many lab pathologists or their directors have made the decision to develop their own test as an alternative to a commercial companion diagnostic test. Lab developed tests, or LDTs, are quite prominently utilized in the oncology space in Canada, and therefore, labs are essentially operating as diagnostic technology companies. Financial support is required through the drug approval process to bridge the funding recommendation to the siloed budget considerations of the drug and its associated companion diagnostic.

At the hospital level, hospital laboratories are the gatekeepers for access to a companion diagnostic. The realities of diagnostic testing in a public healthcare system can be quite sobering. Hospital laboratories have finite budgets: listing a new diagnostic test can mean delisting another and “*taking away health from someone else*.”<sup>13</sup> In addition to the acquisition costs of the test kit, there are also system-wide costs they must take into consideration, including labour, IT infrastructure, knowledge, and capital investment. Alberta has adopted a stepwise iterative process for making decisions on diagnostic test listing, delisting and usage. This is discussed in greater detail in Section D below.

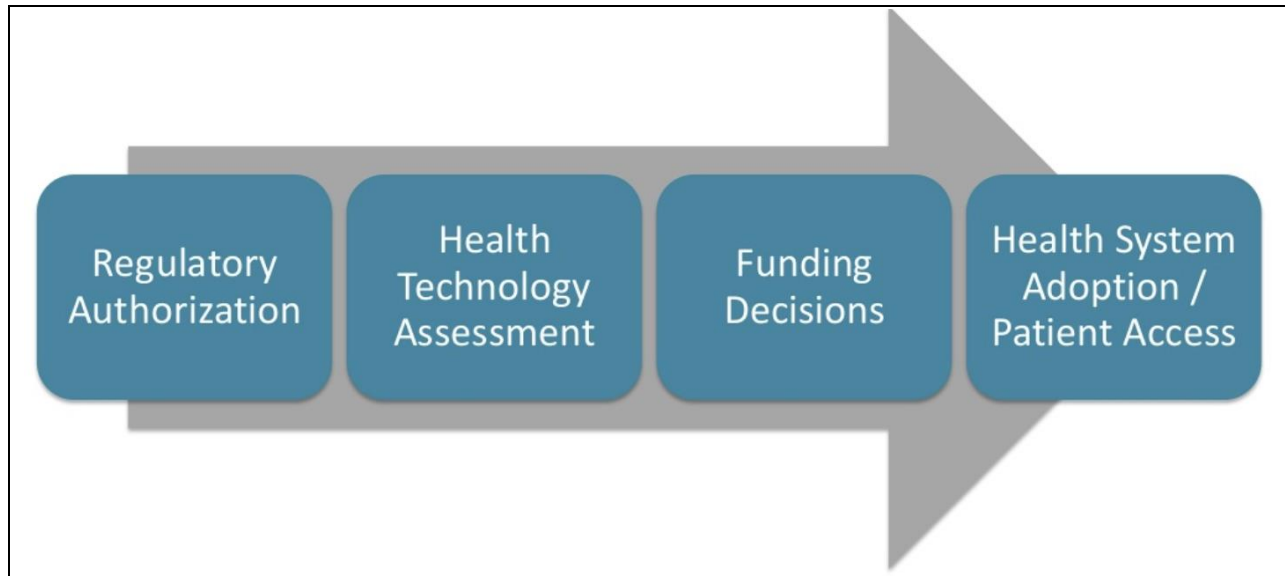
Stakeholders also identified a lack of a well-defined provincial process to evaluate companion diagnostics. And when provincial reviews are completed, there is duplication amongst the provinces. Subsequently, this prevents timely decision-making regarding companion diagnostic funding and delays patient access to required testing.

The above-noted stakeholder feedback may point to support for a centralized structure for funding of companion diagnostics to ensure the quality of tests offered and consistency in patient access to this technology is in place across Canada. Concerns regarding cross jurisdictional inconsistencies in the processes for approving, reimbursing and accessing companion diagnostic tests can create confusion among patients and clinicians regarding the availability of such tests.

Pan-Canadian governance is required to oversee a centralized process in the development and implementation of an informed public reimbursement decision-making system for companion diagnostic tests.

### C. HEALTH SYSTEM ADOPTION PATHWAY

In Canada, companion diagnostic tests follow a varied and complex path to healthcare system adoption and patient access, as the previous two sections (Health Technology Assessment & Funding) have illustrated (Regulatory Authorization to follow below):



The issues identified in the literature on the current healthcare system adoption pathway for oncology drugs and their companion diagnostics ranged from interprovincial variability in regulations and operations to issues that impact companion diagnostic uptake to separate approval pathways for the oncology drugs and their companion diagnostics. One of the issues cited is the fact that drugs and companion diagnostics (both LDTs and IVDDs) undergo a different approval pathway in Canada, resulting in disjointed coverage or lack of access for patients. The drug may become available to patients long before the companion diagnostic becomes accessible. Patients may, therefore, bear the burden of having to access the companion diagnostic on their own for a fee, which might be a significant, out-of-pocket expenditure for some patients.

The lack of a national, harmonized pathway was a major concern throughout the literature and was also identified by interviewed stakeholders. From a regulatory perspective, a companion diagnostic is considered an IVDD and is submitted separately from its corresponding drug product. As noted earlier in this paper, IVDDs are regulated through the Medical Device Bureau of the Therapeutic Products Directorate (TPD), and the drug product is regulated by the TPD or the Biologics and Genetics Therapies Directorate (BGTD). Although difficult to coordinate, the review process should occur in parallel to ensure that the drug and companion diagnostic receive marketing authorization at the same time. In addition, it is advisable that the IVDD is part of the corresponding drug product pivotal studies, and the IVDD and drug product are written into each other's label, to optimize the use of the matched companion diagnostic in clinical practice.<sup>13</sup> However, the majority of companion diagnostics in Canada are LDTs, which do not undergo any federal regulatory approval.

Currently, health technology assessments (HTAs) are used to inform reimbursement recommendations for companion diagnostics, but in addition to CADTH, the HTA may come from a variety of sources: provincial HTA agencies, provincial ministries of health, and hospitals. Once a recommendation has been made, funding for a companion diagnostic may come from different sources, including those identified in Figure 8 below:



**Figure 8: Funding Sources for Companion Diagnostics in Canada**

In Canada, labs are developing their own companion diagnostic tests (LDTs). Some may argue the existence of LDTs is reason alone not to invest funding into the pre-launch of companion diagnostic tests. Why increase awareness of a specific companion diagnostic test if an LDT will be used instead of the regulatory approved companion diagnostic test launched with a particular drug? However, it is not the test itself that matters in the end. What matters is that the test is administered, and that the appropriate patient population is identified so that the treatment can be delivered to the suitably identified patients. Ideally, this will benefit all stakeholders.

National harmonization of clinical laboratory tests may, therefore, improve the efficiency of the clinical diagnostic testing landscape. Incorporating harmonization of LDTs into any future legislative regulatory framework will require the standardization of LDTs, with evidence of concordance with each other and with IVDDs.<sup>12</sup>

As a result of the lack of standardization of companion diagnostic testing in Canada and the lack of national harmonization overseeing diagnostic testing, there are inconsistent practices and approaches among provincial jurisdictions and institutions resulting in duplication of efforts and barriers to the creation of standardized policies for each jurisdiction. In light of the different approaches to regulating and reimbursing companion diagnostics and the fact that the Canadian regulatory environment has not kept pace with the advances in precision medicine, there may be an absence of clear health system adoption pathways throughout the country.

Since regulation of diagnostic services is at the provincial level, hospital and HTA-based decisions differ within each province, resulting in inconsistent, varied regulatory frameworks and approaches to

companion diagnostic testing across Canada. The result: the healthcare system adoption pathways in Canada are not clear and they are ill-defined for companion diagnostic tests.

In addition, valuable resources are required to make companion diagnostics available to the patients who require them for treatment candidacy. Data to support the value and utility of these tests is clearly important, but the criteria utilized to support their utility may vary from province to province and may, therefore, be ill-defined. Payers may place the burden on drug manufacturers to bear the costs of data and analytics. Clearly, additional funding is required to support timely implementation and access to these diagnostics. *“Hospitals are under pressure to make new companion diagnostics available with their corresponding drugs but may not receive extra funding to do so.”*<sup>8</sup>

**Brandon Levac**, representing Bayer Canada, commented on the challenges related to implementing or accessing companion diagnostics in Canada and provided the following thoughtful solution in terms of resources:

*“Increase funding for testing within Ministry of Health budgets – need for testing will only increase in the future.” And, “For new, non-proprietary diagnostics, it would be good if standards are established on the HTA/funder side for validation and determination of clinical utility. It would be fair for a drug manufacturer to support the research in establishing this with the pathology labs, and perhaps in doing so, providing interim funding for the testing. Following this, there should be a transparent process towards funding of the diagnostics.”*

CADTH could not be interviewed but did provide the following thoughtful reply in writing when asked if standardized methods for reimbursement of diagnostic tests were lacking in Canada:

*“As the healthcare system is administered by the individual provinces and territories, standardization of reimbursement processes and methods for companion diagnostic testing would require co-ordination and joint decision-making across the various health ministries and agencies. In addition to clinical utility, these decisions would include other factors, including the priorities and resources (similar to drug reimbursement decisions).”* **Trevor Richter, Director, Pharmaceutical Reviews, CADTH**

Stakeholders also identified the provincial differences in terms of implementation, which is particularly pronounced when there are multiple drugs with multiple tests for the same indication, as well as multiple versions of the same tests available. Implementation includes standardization of test validation, thresholds to be utilized, and results interpretation.<sup>9</sup>

#### **D. HEALTH SYSTEM DELIVERY**

Stakeholders thoughtfully identified some key challenges in the actual delivery of the companion diagnostic testing in Canada’s provincial health care systems. The most notable challenge described by all stakeholders was how the system needs to change to reflect the rapid development of molecular biomarker testing. The pace of biomarker discovery (and the consequent development and approval of biomarker-based treatments) has increased exponentially, which has ushered in the era of the highly sought-after precision medicine by patients.

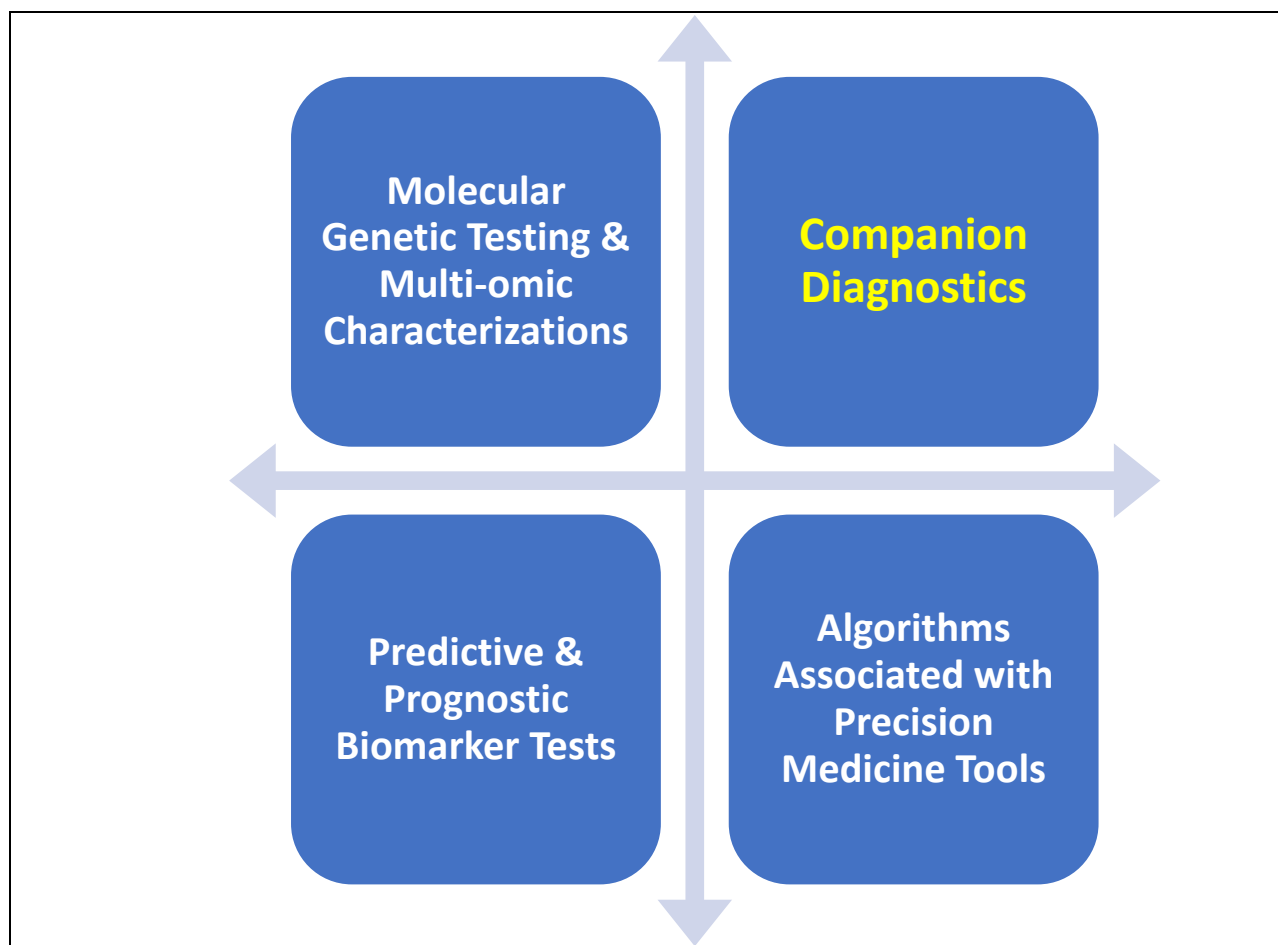
Stakeholders also described some of the uncertainty surrounding the use of LDTs which are not subject to regulatory approval when compared to their approved counterparts, IVDDs. A recent commentary appearing in CMAJ called for Health Canada’s leadership in the regulation of laboratory-developed tests, as it claims to have revealed a weakness in Canada’s regulatory system overseeing approval of these

laboratory developed tests. *“Such tests are not subject to Canada’s statutory regulation of medical devices for safety and efficacy, but they are widely used in Canada’s health care system. Absent regulation as medical devices, the only controls on test performance are laboratory regulation and accreditation, which are heterogeneous and sometimes flawed and do not necessarily include assessment of test validity, safety and efficacy.”*<sup>14</sup>

Lack of coordination among the various laboratories and inconsistencies in practices and tests offered were also noted – not only from province to province, but within each province as well. The lack of coordination within the system is a direct result of siloed behavior and thinking among the various stakeholders: drug manufacturers, regulators, HTA authorities, funders/payers, public policy makers, pathologists/laboratories, etc. While all stakeholders may have the best interests of patients in mind, they may behave or think in a siloed manner, which perpetuates the challenges to clinical implementation of companion diagnostic tests. Instead, they should be assuming a collaborative and collective mindset, where stakeholder relationships are built and fostered on the desire to see patients gaining access to a validated, standardized test in the timeliest manner possible.

A lack of funding for the laboratory was also identified as a challenge to clinical implementation. *“There is almost an oppositional approach, where oncologists are requesting biomarkers to best treat their patients, but the laboratory is not funded to provide the test and looks to avoid costly molecular biomarkers...all the while a patient is waiting to see if they are eligible to receive the drug or enter a clinical trial.”* **Dr. Aaron Pollett**, Provincial Head, Pathology & Laboratory Medicine, Cancer Care Ontario.<sup>15</sup>

On February 5, 2020, the Ontario Institute for Cancer Research and Cancer Care Ontario co-led a provincial effort to address the adoption of challenging technologies and processes in Ontario to support health system transformation. This included the following four component areas which captured companion diagnostic testing (please see Figure 9 below):



**Figure 9: Precision Medicine Tools Discussed at the OICR February 5, 2020 Workshop**

The workshop generated a 124-page report clearly highlighting “*precision approaches to healthcare representing a major paradigm shift in oncology research*” and representing ... “*a significant health system adoption challenge for patient care.*”

A perspective from the Alberta Health Services System was presented as an example where a single diagnostic lab service provider for the entire province was utilized in Alberta. **Dr. Christopher McCabe** was the presenter. “*Alberta Public Laboratories are a single diagnostic lab service provider for the entire province. It created a lab formulary committee and process to add new tests for the province. This includes a formal Health Technology Assessment (HTA). A current HTA nearing completion is looking at two cancer tests (an innovation and an existing, approved test) in which the assessment included the consideration of change management costs to have the health system convert to a new system.*”<sup>15</sup>

Dr. McCabe described how Alberta Health Services (AHS) is moving from an industry push system to a health system pull approach, where clinical need drives innovation. AHS uses an Innovation to Action Lifecycle which matches the needs of the system with the solutions that are available.



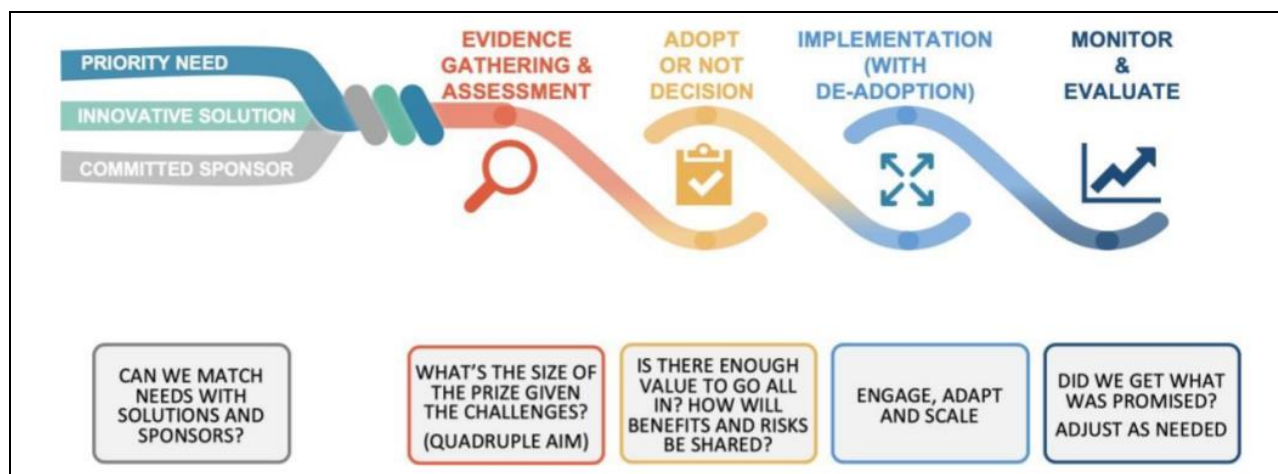


Figure 10: Alberta Health System - Innovation to Action Lifecycle

BioCanRx Review identified a duplication of efforts and expertise resulting from the lack of coordination among the various laboratories.<sup>8</sup> Their respective existing knowledge and expertise were difficult to link as a means to support each other and avoid duplication of efforts for the centralization of specialized laboratory services.

## E. REGULATORY AUTHORIZATION

Prior to being available for patient treatment, an oncology drug must receive regulatory authorization from Health Canada, through which the regulator asks whether the drug is safe, effective and meets quality standards in compliance with the Food and Drugs Act and Food and Drug Regulations. Applications for a notice of compliance (NOC) permitting the drug to be sold in Canada are reviewed by either the Therapeutic Products Directorate (for pharmaceutical products) or the Biologic and Genetic Therapies Directorate (for biologic products) within Health Canada.

Companion diagnostics produced by a biopharma company, such as an in vitro diagnostic device, are considered medical devices and regulated by Health Canada. Medical devices are regulated under the same Act and overseen by the Medical Devices Regulations. The Medical Devices Bureau within Health Canada reviews medical device licence applications.

Currently, there is no formal process for a drug to be reviewed by the regulator along with the companion diagnostic. Where a manufacturer submits a drug and companion diagnostic test kit (considered a medical device) for review, each is subject to different regulations and reviewed by different directorates within Health Canada. When a drug relies on a companion diagnostic, this would be reflected in the drug's product monograph. However, Health Canada does not require the drug to be used with its companion diagnostic as part of its indication. Further, there may be a gap between authorization of the drug and authorization of the device. Laboratory tests that are developed in-house by laboratories may be used as companion diagnostics but are not regulated by Health Canada as medical devices. There is no regulation of laboratory services at the federal or national level, although laboratories may wish to be accredited against extensive standards established by Accreditation Canada.<sup>8</sup>

It is unfortunate that despite multiple requests, Health Canada did not respond to any of the telephone or email requests for an interview on the regulatory pathway overseeing companion diagnostic testing in Canada. The author regretfully cannot incorporate the Health Canada perspective in this report.

Stakeholder perspectives on the regulatory environment overseeing companion diagnostic testing included:

- The need for more clarity on what Health Canada is doing from a regulatory perspective.<sup>15</sup>
- Laboratory-developed tests are not regulated by Health Canada.<sup>8</sup>
- There is a lack of transparency, clarity and rationale for restrictions overseeing lab test licenses: the process is unclear and there is no timeline for approval.<sup>15</sup>
- No Canadian entity is formally responsible for independently evaluating the development, validity or adverse events of tests delivered by laboratories, unless they are marketed as test kits and reviewed by Health Canada.<sup>14</sup>
- Regulatory authorization of drugs and companion diagnostics are separate processes.<sup>9</sup>
- Lack of standard language regarding companion diagnostic on product labelling.<sup>9</sup>

The Canadian Medical Association Journal (CMAJ) paper<sup>14</sup> relayed what it considered to be a serious concern on the absence of regulatory approval for LDTs. These tests are not subject to Canada's statutory regulation of medical devices for safety and efficacy, but they are widely used in Canada's healthcare system. The CMAJ authors maintain the only controls on LDT performance are laboratory regulation and accreditation, which are heterogeneous and sometimes flawed and do not necessarily include assessment of test validity, safety and efficacy. The CMAJ authors strongly stress: *"Regulators in Australia, the United States and Europe have made efforts to close this 'gaping regulatory loophole,' but Health Canada has not indicated that it plans to do the same. In the interests of the nation's health, it should."*<sup>14</sup>

**Dr. Aaron Pollett**, Pathologist and lab director at Sinai Health Systems, was asked to comment on and respond to the CMAJ position paper. While respectful of the authors' position, he did not share their view. He could not speak to the processes and accreditation practices in other provinces, but he certainly stood by the LDT controls, performance, validity, safety and efficacy in Ontario and specifically in his lab. He provided a description of the Biomarker Community of Practice in Ontario:

*"In Ontario, Ontario Health-Cancer Care Ontario oversees the funding and oversight of biomarkers associated with therapy (companion diagnostics). For all funded biomarkers, there are identified reference sites which act as a provincial resource related to the biomarker. In addition, all funded sites are expected to participate in a biomarker community of practice. These communities of practice bring together clinicians (identified through the relevant tumour site groups and medical oncology program) and testing labs to ensure that the testing meets clinical needs. As part of the community of practice, future directions are discussed so that all testing labs provide all necessary testing, and there is a forum for discussion of any issues related to test characteristics or performance."*

**Dr. Pollett** went on to say: *"There are controls in place overseeing the performance of LDTs, established by Accreditation Canada who has extensive standards in place. And LDTs do undergo careful review, whose findings appear in scientific journals and/or are widely endorsed by clinical practice guidelines."*

## F. LABORATORY OVERSIGHT & OPERATIONS

A lack of national standards guiding laboratory services was identified as an issue by some stakeholders in the literature and by some interviewed on the phone. LDTs are not subject to Health Canada review or any form of federal regulation. The current Canadian laboratory regulatory system involves a mixture of public and private entities and operates with oversight from provincial governments, non-governmental organizations, and professional societies. Most provinces and territories rely on voluntary standards that are unevenly applied, with little auditing and systematic testing to ensure quality. The current lab regulations in Canada apply only to the operations of the medical laboratories themselves, encompassing such things as lab environments, personnel, accreditation, and quality control.<sup>16</sup>

The authors of the CMAJ paper are calling upon Health Canada to take steps to regulate LDTs in Canada, for there currently is no government agency responsible for the oversight of LDTs. Only LDTs that are marketed as test kits are evaluated and reviewed by Health Canada.

As more LDTs are developed and manufactured, however, it is probable that provincial governments will continue to evaluate the administration and oversight of LDTs, assuring that each province has its own licensing and lab accreditation system in place. A concerted pan-Canadian effort would be required to harmonize and standardize laboratory services across Canada.

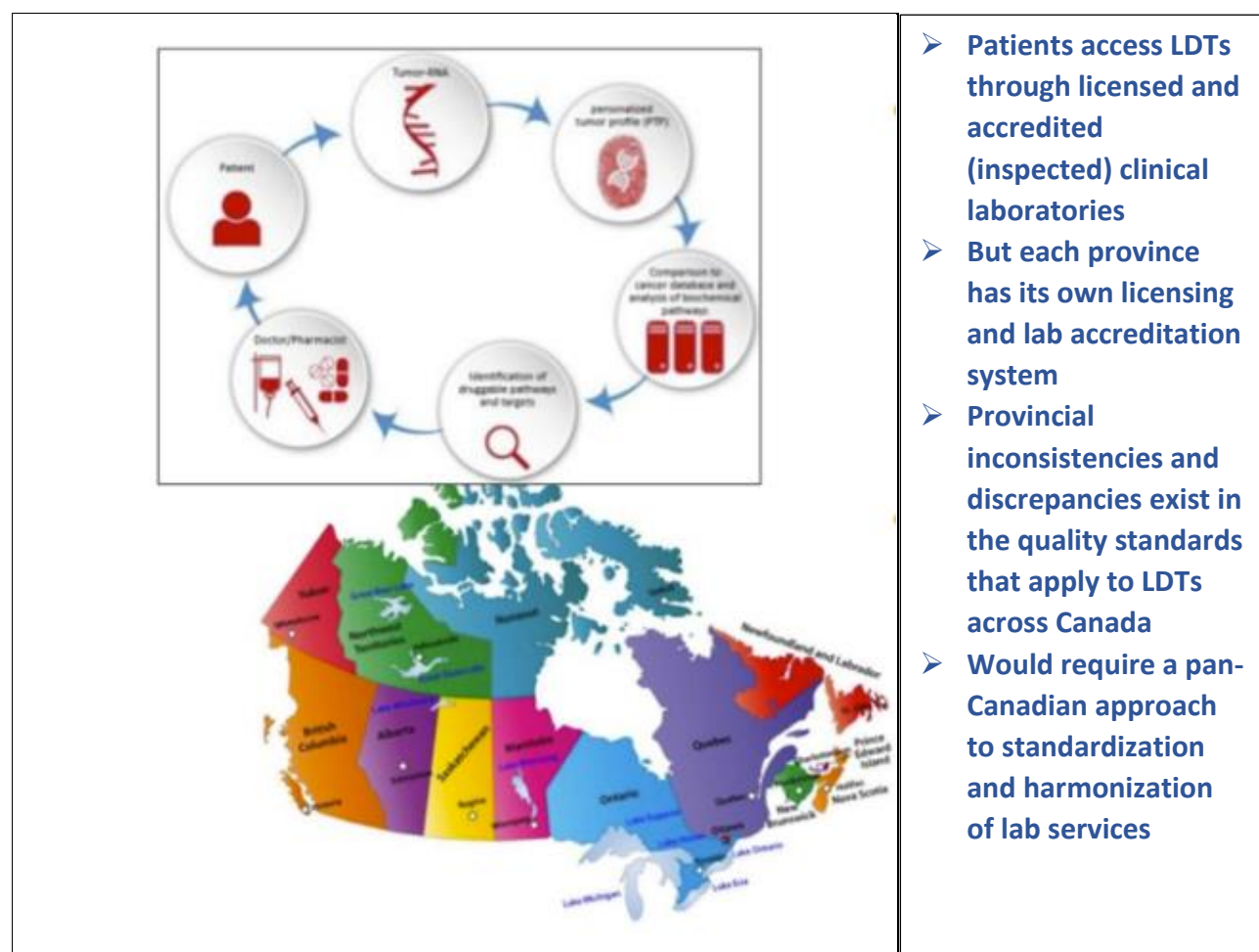


Figure 11: Interprovincial Variability across Canada Regarding Quality Standards of Lab Tests

In 2016, the Canadian Agency for Drugs and Technologies in Health (CADTH) issued a report based on an environmental scan of pharmaceuticals requiring companion diagnostics to inform Canadian policymakers. Their report was published in the *International Journal of Technology Assessment in Health Care*. Their scan was based on a focused literature search and feedback solicited from targeted stakeholders. On the issue of laboratory operations and oversight, the authors said:

*“Quality assurance of companion diagnostics is also important, although not directly regulated by Health Canada. As the number of drug treatments for which genetic testing is required increases, access to reliable high-quality testing must be ensured to maximize the benefit that can be derived from personalized medicine. Reliability and quality of testing can be assured through an established effective framework for clinical laboratory operation, 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 frameworks across the provinces and the lack of national oversight or guidelines to facilitate harmonization and good practice in laboratories throughout Canada (19). Stakeholder feedback was received concerning the potential need to provide information on the legal implications to Canadian healthcare institutions and their laboratories of using proprietary Companion diagnostics, or equivalent laboratory developed tests (LDTs), including on and off-label uses of such tests.”<sup>18</sup>*

The BioCanRx Paper identified two concerns from seven stakeholders:

- Insufficient oversight, standardization, and harmonization across Canada: no national standards that guide laboratory services: “...some national requirements for clinical laboratory accreditation applicable to LDTs should exist.”
- Laboratory-developed tests are subject to low quality standards: the uneven oversight of laboratory operations across Canada is particularly pronounced in the discrepancy between the quality standards that apply to LDTs and those that apply to diagnostics regulated by Health Canada.<sup>8</sup>

Since LDTs are designed, manufactured, and used in a laboratory setting, they are not meant to be sold as standalone kits. They are regulated by provincial regulations relating to laboratory safety and quality. Accordingly, all laboratories offering diagnostic testing are required to obtain an operation licence issued by the provincial Minister of Health, as well as self-regulated accreditation and quality controls. Because each province has its own regulations relating to medical laboratories, these rules have been shown to vary considerably from one provincial jurisdiction to another. In some provinces, there is a lack of binding rules whereas other provinces have developed elaborate legal frameworks.

Given that diagnostic testing is offered predominantly as a laboratory service and given the variations between provincial regulations on LDTs in Canada, harmonized oversight of diagnostic tests has been proposed, particularly for high-risk LDTs. At present, LDTs that are considered to pose a high individual risk (i.e. equivalent to Class III devices) are not required to comply with Health Canada regulations which may be more stringent. The Canadian regulatory frameworks relevant to precision medicine technologies are complex, owing in part to the division of powers between the federal and provincial governments.<sup>17</sup> It remains to be seen whether regulatory harmonization might be on the horizon, and whether harmonization would address the regulatory challenges. One thing, however, is clear: a national, concerted effort is required by all stakeholders to achieve this highly sought after ideal.

**Jill Hamer-Wilson** was the Canadian Clinical Trials Group (CCTG) Lung Cancer Patient Representative and kindly agreed to be interviewed on the phone. She provided a meaningful perspective both from the

patient and CCTG viewpoint. When asked about any challenges or barriers to accessing companion diagnostic testing, she provided the following thoughtful reply:

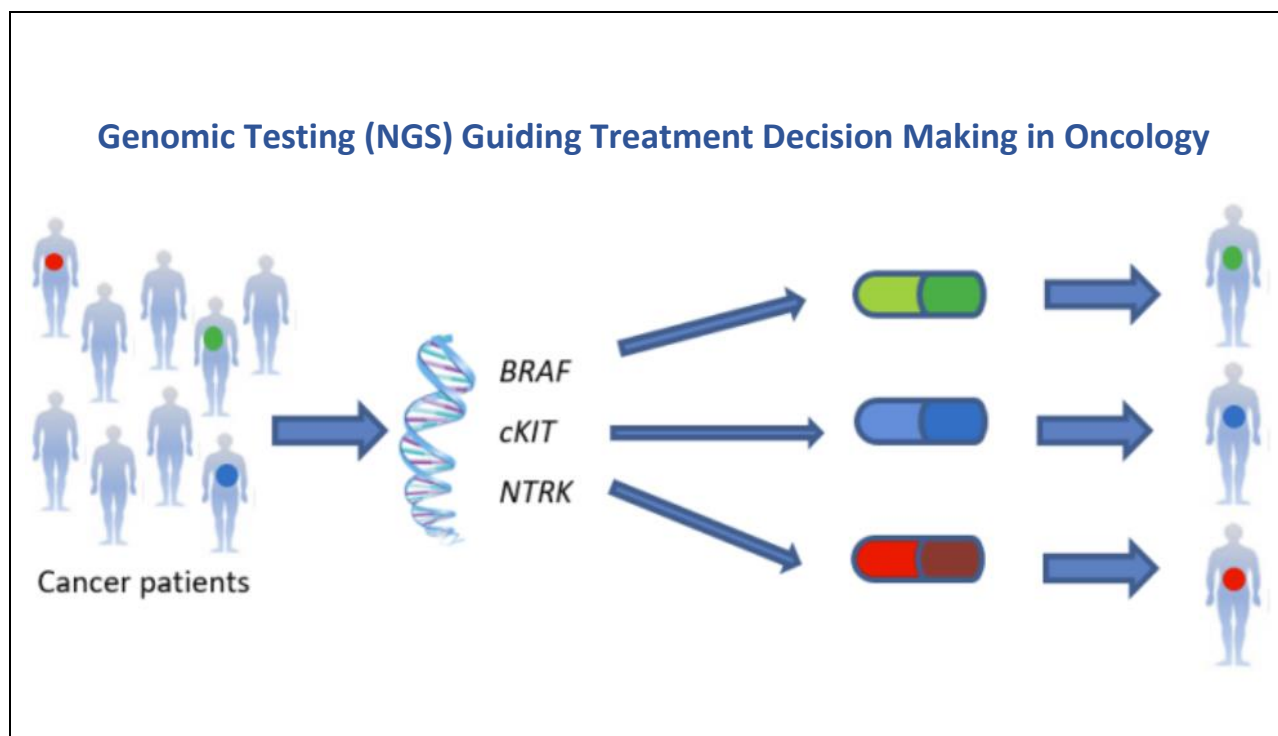
*“I believe Canada has a patchwork process in place when it comes to accessing companion diagnostics. There is no regulatory board in place overseeing the tests and it varies from province to province and hospital to hospital. Every cancer patient should be tested for every available biomarker. Not doing so is unconscionable! As you know, the most stressful times in a cancer patient’s journey, from a psychosocial standpoint, is when the diagnosis is delivered and when there is disease progression. So receiving the results of companion diagnostic testing in the timeliest fashion possible as soon as a patient is diagnosed is critical, for it can ease some of that stress. But there needs to be accountability for biomarker testing and those tests need to be regulated across the country. And there needs to be comprehensive testing performed – not a singular individual test.”*

**Jill Hamer-Wilson’s** compelling statement will allow this author to dive into the next section of this paper, which deals with increasing demand for next generation sequencing.

#### **PART IV: FROM COMPANION DIAGNOSTICS TO GENOMIC PROFILING - NGS**

Second generation sequencing technologies, commonly referred to as Next Generation Sequencing (NGS), have been developed in an effort to enable the routine genomic study of every tumour. NGS allows for rapid and accurate sequencing of many genes at once, utilizing either DNA or RNA. For most clinical applications, NGS uses gene panels to sequence only a discrete number of genes of interest, making it less labor intensive than complete DNA or RNA sequencing methods.

With these larger panel tests entering the market in oncology, patients may access a test that can be administered at the time they are being worked up for diagnosis where they can test hundreds of different biomarkers. These tests are becoming more readily available, and test smaller samples for a wide array of markers in one panel.



**Figure 12: Genomic Testing Guiding Treatment Decision Making in Oncology**

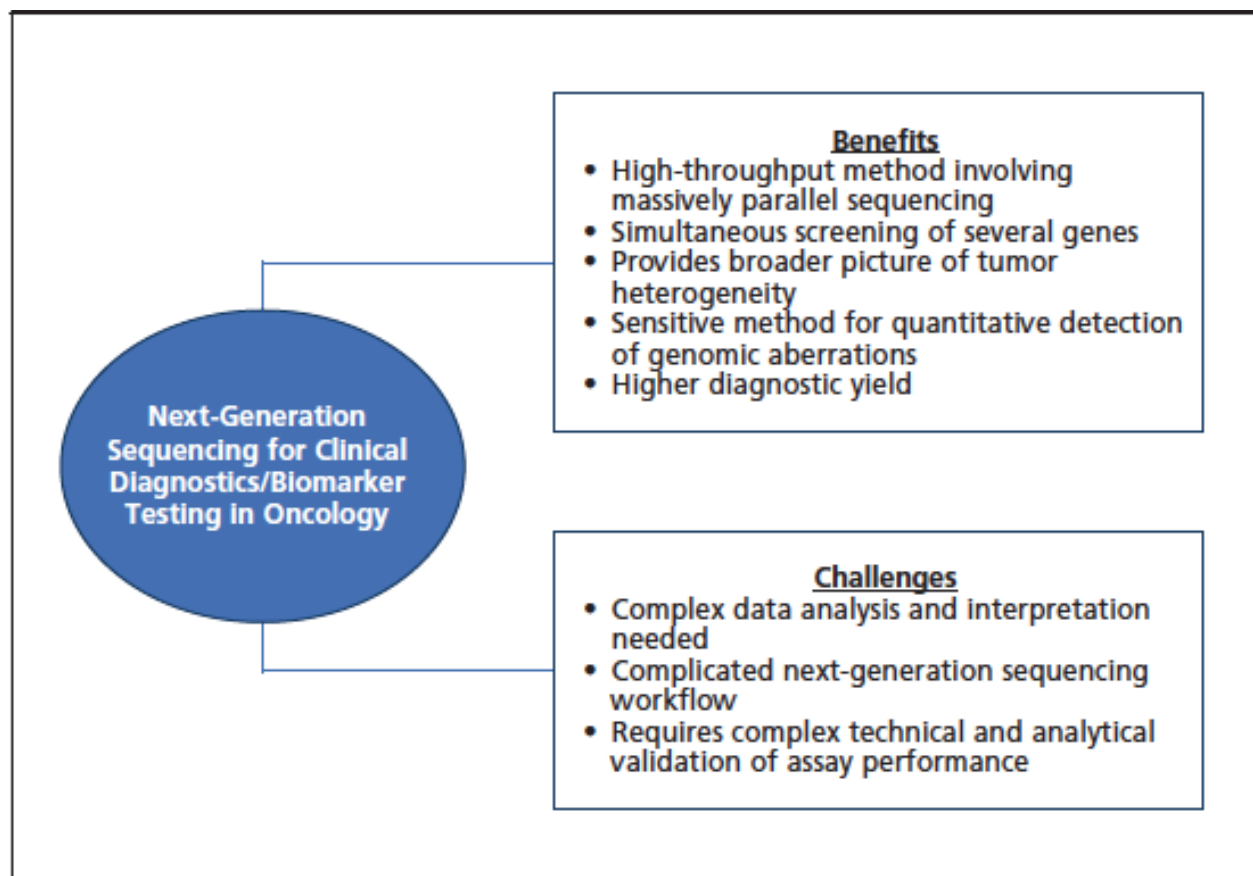
A Canadian guideline on the use of NGS in oncology was published in April 2019. It was developed by a steering committee of pathologists, geneticists, oncologists, and genetic counsellors from across Canada.<sup>19</sup> It provides guidance for oncologists on the use of NGS for the identification of somatic variants in adult cancers. A number of targeted therapies have been approved in Canada for use in patients harbouring specific gene variants. By correctly identifying patients who might respond to those agents, oncologists can both treat those who could derive benefit and spare those who are unlikely to benefit from unnecessary toxicities and unwarranted costs. Moreover, NGS can be used to identify patients who could be susceptible to drug toxicities. For example, patients with germline variants in the *DYPD* gene are at risk of toxicity from 5-fluorouracil, resulting in greater neutropenia, mucositis, and diarrhea. For patients who experience disease progression, NGS can then prove useful in the detection of resistance variants that might cause treatment failure to guide selection of subsequent therapies. For example: *KRAS*, *NRAS* and *BRAF* variants are associated with resistance to therapy targeting *EGFR*.<sup>19</sup> Patients may also proceed to a clinical trial based on the identification of a driver alteration from the results of NGS testing once standard of care therapies have been exhausted.

Early testing is important to ensure prompt and effective treatment, especially for aggressive cancers. For example, **reflex testing**\* including multiple genes has been shown to save valuable biopsy tissue and to reduce time to treatment for patients with lung cancer. In those patients, whose prognosis is typically poor, reflex testing (compared with on-demand testing) has been shown to provide more timely access to treatment. The advantage of NGS compared with single-gene testing is that NGS has the ability to screen for a broader set of variants in one complete test, making the most efficient use of limited biopsy tissue. In addition, when multiple genes are tested, greater cost-effectiveness has been shown for NGS compared with sequential single gene testing modalities. Given an increase in clinically validated biomarkers and a reduction in cost and testing time, the benefits of NGS are expected to grow. However, the use of NGS in place of companion diagnostic tests depends on the funding of NGS-based testing across Canada, for which no process is currently defined.<sup>19</sup>



[\*NB: Lung Cancer Canada refers to **reflex testing** on their website as part of the patient's diagnostic workup and provides the following definition: "Reflex Testing involves performing testing for currently known lung cancer mutations or drivers at the same time that the diagnostic testing is carried out, irrespective of the patient's tumor staging."]<sup>20</sup>

When comparing NGS to IHC or FISH, NGS has the advantages of high speed, high throughput, and high accuracy (please see **Figure 13 below**). Traditional molecular assays focus on only a relatively small panel of genes that are known to harbour common alterations (referred to as hotspots). In contrast, NGS simultaneously characterizes many genes in the same assay, provides a broader picture of genetic heterogeneity, and allows for quantitative and sensitive detection of genomic alterations that otherwise may not be tested.<sup>21</sup>



**Figure 13: Benefits & Challenges of NGS for Clinical Diagnostics & Biomarkers Testing in Oncology**

An online commentary on precision medicine and companion diagnostics by Michele Clearly showcased the importance of proceeding from single gene panel testing to large panel testing with caution:

*"In the early days of precision medicine, we were targeting individual markers – EGFR, ALK, HER2, etc. And that's still the preponderance of what's on the market. But where we are going, and we are getting closer and closer, is hitting a tipping point...Where we are headed, though, is for a test to be administered at the time the patient is being worked up for diagnosis where we could test hundreds of different biomarkers. Those tests will redefine what good looks like in precision medicine once they gain full acceptability. Next generation testing – larger panel tests including dozens of common biomarkers are now more readily available, testing smaller samples for a wide array of markers in one panel. It is*

*reconciling our ability to know more biomarker information and then how to pull it through to a patient's treatment approach. ...But we are working with complex things that we understand only a small part of. That always carries risk. But that doesn't mean you don't go there; it just means that you just go with appropriate caution and be prepared for the results not to be quite what you expected."*<sup>22</sup>

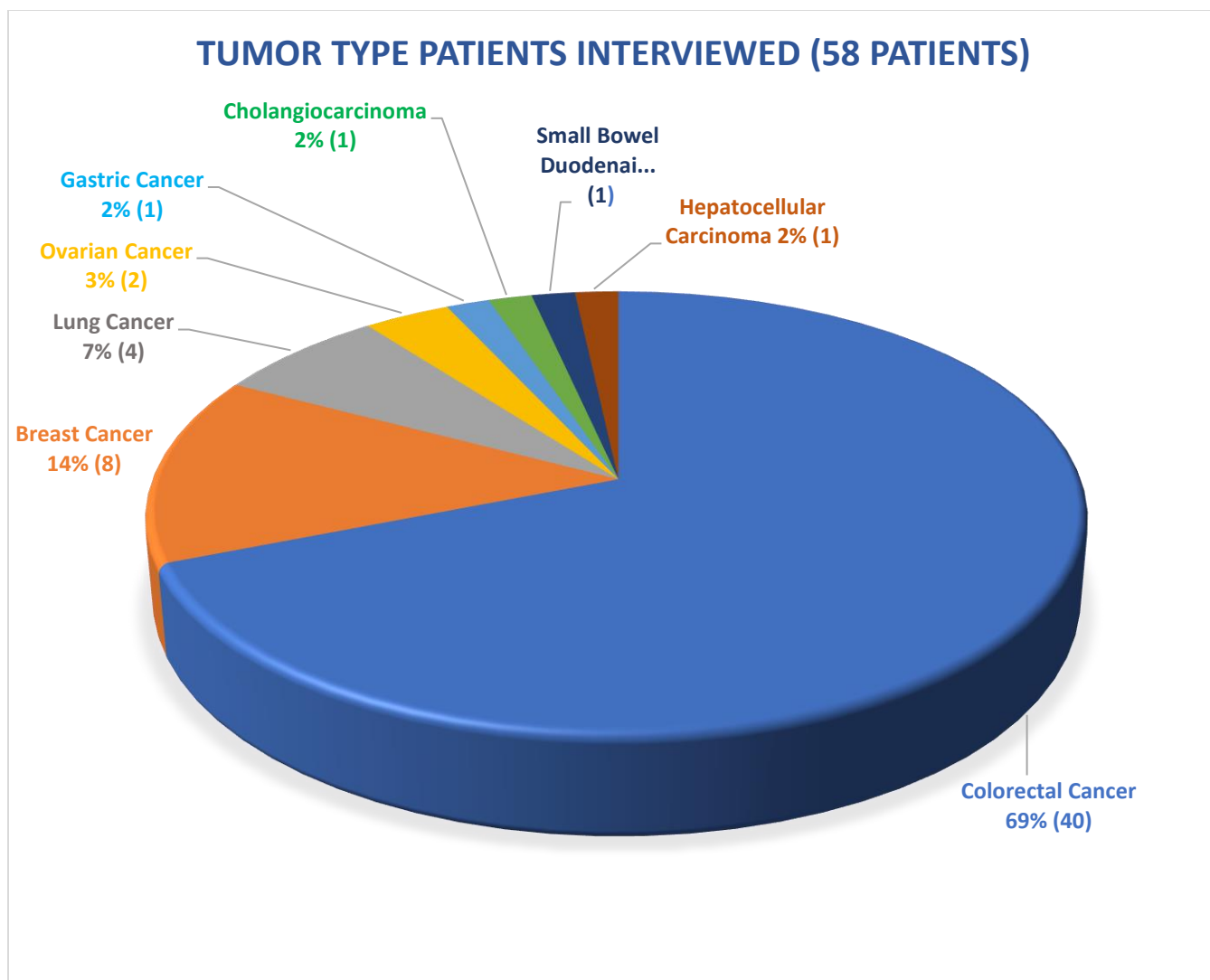
More than ever, patients are engaged, knowledgeable, and equipped to participate in and contribute to their cancer care, and most treating oncologists value that patient participation. This patient-clinician dialogue highlights a true partnership in the fight against and management of cancer. Patients partnering with their clinicians allow for shared decision making and more informed decisions to be made that are consistent with patients' needs, values, and preferences.

As cancer patients learn of NGS testing, it is not surprising of their desire to actively seek out this revolutionary testing option for various reasons.

**Dr. Robin McGee**, a Halifax-based Stage 4 rectal cancer patient who provided a great deal of insight into her cancer journey, expressed her need to access NGS testing in Calgary, Alberta, as an out-of-pocket expense to help inform her treatment decisions in an effort to gain access to precision medicines that would directly target the mutations in her metastatic rectal cancer. She states:

*"Years ago, I knew a patient who battled cancer for ten years and another who had the same cancer but died within weeks. There is clearly a biological reason for that. Now we have a means to determine why that is and can help patients and oncologists determine which patients should avail themselves of certain therapies and who should clearly refrain from them because they will not benefit from them and will therefore avoid unnecessary treatment toxicities. The more biological information we have at hand, the more ammunition we have to treat the disease by identifying the various subtypes of cancer and genetic alterations. There needs to be a massive investment in not only companion diagnostics but in NGS testing in all provincial jurisdictions."*

To further capture cancer patients' perspective on NGS testing, fifty-eight cancer patients were interviewed on the phone between July 1 and August 10, 2020. Tumor type distribution was as follows:

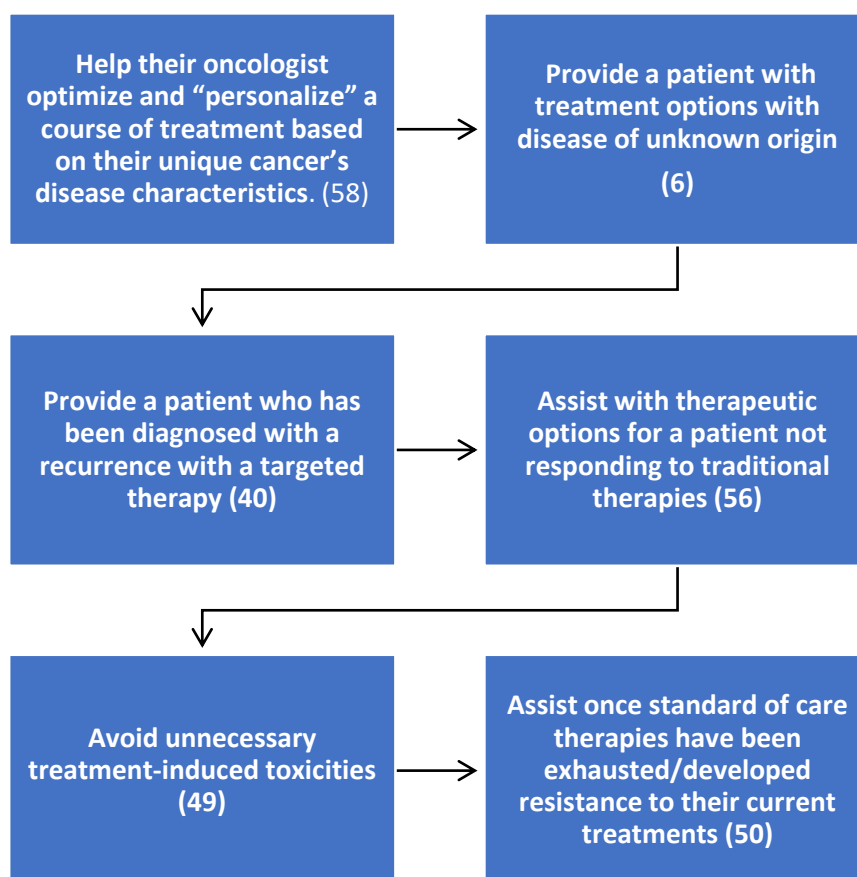


**Figure 14: Tumor Type Distribution**

Patients were asked the following question:

**“What do you believe Next Generation Sequencing Testing can accomplish for you or other metastatic cancer patients?”**

The results of the telephone interviews are summarized below in **Figure 15**. Patients believe the information generated from the test results can:



**Figure 15: Metastatic Cancer Patient Perceptions Regarding NGS Testing**

60% of patients interviewed on the phone had already accessed NGS testing through a clinical study at their treating centre, such as OCTANE, or as an out of pocket expense (through Foundation One, OncoHelix, or Caris) to help inform and guide treatment decisions. Patients are looking to avail themselves of every tool in the arsenal of treatments to help improve outcomes. There are, however, challenges surrounding NGS testing that must be overcome on a national level from a multi-stakeholder perspective. These challenges include clinical research, regulatory approval processes and reimbursement as well as a myriad of other concerns that will impact patient access and sustainable innovation.

As stakeholders come together to discuss the standardization of companion diagnostics resulting from the recommendations appearing in the next section, perhaps consideration can also be given to the role NGS Testing should play in the Canadian landscape in the near future.

## PART V: RECOMMENDATIONS

The recommendations presented below have been organized according to the six categories of challenges identified in the literature and by interviewed stakeholders. The recommendations are by no means exhaustive. They are intended to guide discussion among the various stakeholders who wish to collaborate in an era guided by precision medicine that has brought about a paradigm shift within the Canadian healthcare system.

## STAKEHOLDER RECOMMENDATIONS RE: COMPANION DIAGNOSTIC TESTING IN CANADA

ISSUE	RECOMMENDATION
<b>A. Health Technology Assessment (HTA)</b>	<ol style="list-style-type: none"> <li>1. Create a pan Canadian common review body to assess diagnostic tests for implementation across Canada. This would allow for increased transparency of process and criteria.</li> <li>2. The best practices of a formal review process (such as the one in place at INESSS), where the oncology drug and its associated companion diagnostic are co-assessed, may be reviewed for potential adoption.</li> </ol>
<b>B. REIMBURSEMENT/ FUNDING</b>	<ol style="list-style-type: none"> <li>1. Bridging the gap between a positive HTA funding recommendation and inter-provincial Companion Diagnostic Test reimbursement uptake across Canada by linking the HTA co-assessment and reimbursement of drug and companion diagnostic.</li> <li>2. Elimination of budget silos could assist with uptake of the companion diagnostic when payers are adding the oncology drug in combination with associated companion diagnostic to their provincial formulary.</li> <li>3. The establishment of a pan-Canadian oversight committee to review, interpret and provide recommendations on the funding, listing and delisting recommendations of each diagnostic across multiple centres in Canada. This might ensure uniform testing across the various provincial jurisdictions and promote standardization of testing.</li> <li>4. Provide funding for every diagnostic test that will be standardized across multiple centres throughout Canada. Clinical utility must be established and validated early on with drug manufacturer collaboration to assist with <u>initial</u> funding early on in the pathway, while restricting the amount of time for pharmaceutical company to fund companion diagnostic testing. Overall, funding must be increased for testing within the <u>Ministry of Health budgets</u> as the need for testing will continue to increase with time.</li> <li>5. Increase evidence-based dis-investment in laboratory testing in order to create headroom for new innovations.<sup>9</sup></li> <li>6. Create an R&amp;D budget for laboratory services that permits the development and validation of laboratory derived tests in order to reduce costs.<sup>9</sup></li> <li>7. Create multidisciplinary provincial working groups, and mechanisms for the provinces to learn from each other, to develop standard protocols/business cases to guide companion diagnostic assessments.<sup>9</sup></li> <li>8. Provide greater analysis from a pan-Canadian body, such as CADTH,</li> </ol>

	<p>to support the provinces with an understanding of the utility and validity of a companion diagnostic, as well as a framework to assess value that includes decision-making considerations and criteria that provide clear expectations for what is acceptable/unacceptable evidence of value.<sup>9</sup></p> <p>9. Create a centralized national laboratory testing.<sup>9</sup></p> <p>10. Develop a harmonized framework for laboratory testing implementation.<sup>9</sup></p>
<b>C. HEALTH SYSTEM ADOPTION PATHWAY</b>	<ol style="list-style-type: none"> <li>1. Support centralized testing for the country. In addition, the development of a harmonized framework for laboratory testing implementation would be helpful.</li> <li>2. Support national harmonization of companion diagnostics to ensure standardization of diagnostic testing across centres and labs. Incorporate harmonization of LDTs into any future legislative regulatory framework. This will require the standardization of LDTs with evidence of concordance with all LDTs across Canada and with IVDDs. Align HTA frameworks across Canada for companion diagnostics and their drugs.</li> <li>3. Ensure a review process occurs in parallel for the drug and companion diagnostic for marketing authorization purposes.</li> <li>4. Increase funding for diagnostic testing within Ministry of Health budgets to support their utility, implementation and access.</li> <li>5. Promote regular stakeholder engagement opportunities to collectively advance companion diagnostic testing in the Canadian marketplace. This could take the form of an advisory body or panel which may wish to address and reverse the inconsistencies in the health system adoption of companion diagnostics across Canada. Interprovincial oversight will improve uptake and promote consistency in clinical implementation and access to companion diagnostics in Canada.</li> </ol>
<b>D. HEALTH SYSTEM DELIVERY</b>	<ol style="list-style-type: none"> <li>1. Coordinate discussions amongst the various stakeholders, engaging them in a full pan-Canadian collaboration – avoid siloed thinking which perpetuates challenges to clinical implementation of companion diagnostic tests.</li> <li>2. Provide a better receptor capacity by a more structured approach to laboratory testing: there are some deficiencies that threaten the delivery of appropriately quality controlled testing, which in turn impacts clinical implementation of and access to companion diagnostic testing. Of concern are tests that are not provided as licensed kits (which are controlled and regulated by Health Canada) that are developed independently amongst the various laboratories. This raises the concern of quality of testing. This is coupled with disparity of funding plus the problem that there is little/no coordination of what test is offered where, leading to possible inequity of access. The excessive cost and potential low quality may hamper the delivery of these diagnostics: <ol style="list-style-type: none"> <li>A. Coordinate the implementation of companion diagnostics within</li> </ol> </li> </ol>



	<p>each province and across Canada. This will help ensure the delivery of these services to the patients who require them.</p> <ul style="list-style-type: none"> <li>B. To ensure the safety and effectiveness of these LDTs, consideration should be given to regulating these diagnostics by Health Canada.</li> <li>C. Increase funding to the laboratories from Ministry of Health budgets to support delivery of diagnostic tests.</li> <li>D. Centralize specialized laboratory services to ensure the highest quality testing and development of practice guidelines for laboratories to ensure consistency across the province and nation.</li> </ul> <ol style="list-style-type: none"> <li>3. Consider other jurisdictions which have made progress in one or more areas identified above (i.e. the Alberta Health System).</li> <li>4. Give thoughtful consideration to the creation of a national companion diagnostic test registry and database where large amounts of data can be collected and stored with its accompanying companion diagnostic for the purpose of evaluating the diagnostic relative to its disease process.</li> </ol>
<b>E. REGULATORY AUTHORIZATION</b>	<ol style="list-style-type: none"> <li>1. Include a requirement for specification of the companion diagnostic used in clinical development in a new drug submission and inclusion in the product labelling.</li> <li>2. Improve quality assurance of diagnostic tests across Canada: An <i>“effective framework for clinical laboratory operations, medical testing and diagnostic devices”</i> could reduce the variability in diagnostic testing across Canada.<sup>8</sup></li> <li>3. Provide clarity on what Health Canada is doing from a regulatory perspective on <b>all</b> companion diagnostics.</li> <li>4. Promote transparency and provide rationale for restrictions on lab test licenses: the process should be clear, there should be a timeline for approval, and a nimble process should be in place.</li> <li>5. Collaboration among institutions and provinces is imperative to avoid perception of poor test quality in labs, thereby adopting a more structured approach to laboratory testing. The concern of quality of testing is coupled with disparity of funding plus the problem that there is little to no coordination of what test is offered where, leading to possible inequity of access.</li> </ol>
<b>F. LABORATORY OVERSIGHT &amp; OPERATIONS</b>	<ol style="list-style-type: none"> <li>1. Health Canada may assume a greater role in the regulation of LDTs by building on the efforts of other jurisdictions, much like it has led the way in drug and device data transparency.</li> <li>2. Increase regulation of quality assurance of molecular testing: <ul style="list-style-type: none"> <li>A. Establish standards and processes for proficiency testing for specific tests and a laboratory quality management program in the form of a national external quality assurance program.<sup>8</sup></li> <li>B. Put into place regulatory scrutiny overseeing how LDTs are conducted.<sup>8</sup></li> <li>C. Oversight of testing sites, methods used by testing sites and adherence to laboratory guidelines and best practices is recommended.<sup>8</sup></li> <li>D. To promote consistency and reduce interprovincial variability in regulations and operations, national requirements for clinical</li> </ul> </li> </ol>

	<p>laboratory accreditation applicable to LDTs should exist and a need for development of national accreditation requirements for clinical laboratories.<sup>8</sup></p> <p>E. Since the process to gain access to diagnostic tests and operations of diagnostic labs can vary dramatically across the provinces, development and implementation of a pan-Canadian proficiency testing program is recommended.<sup>8</sup></p>
<b>GENOMIC PROFILING: NEXT GENERATION SEQUENCING TESTING</b>	<p><i>As NGS has the potential to be adopted into clinical practice due to patient demand, give thoughtful consideration to the clinical utility of biomarkers that can be generated from this technology by hosting a national, panCanadian stakeholder roundtable discussion on the clinical utility of this technology.</i></p>

## PART VI: LIMITATIONS, IMPLICATIONS & CONCLUSION

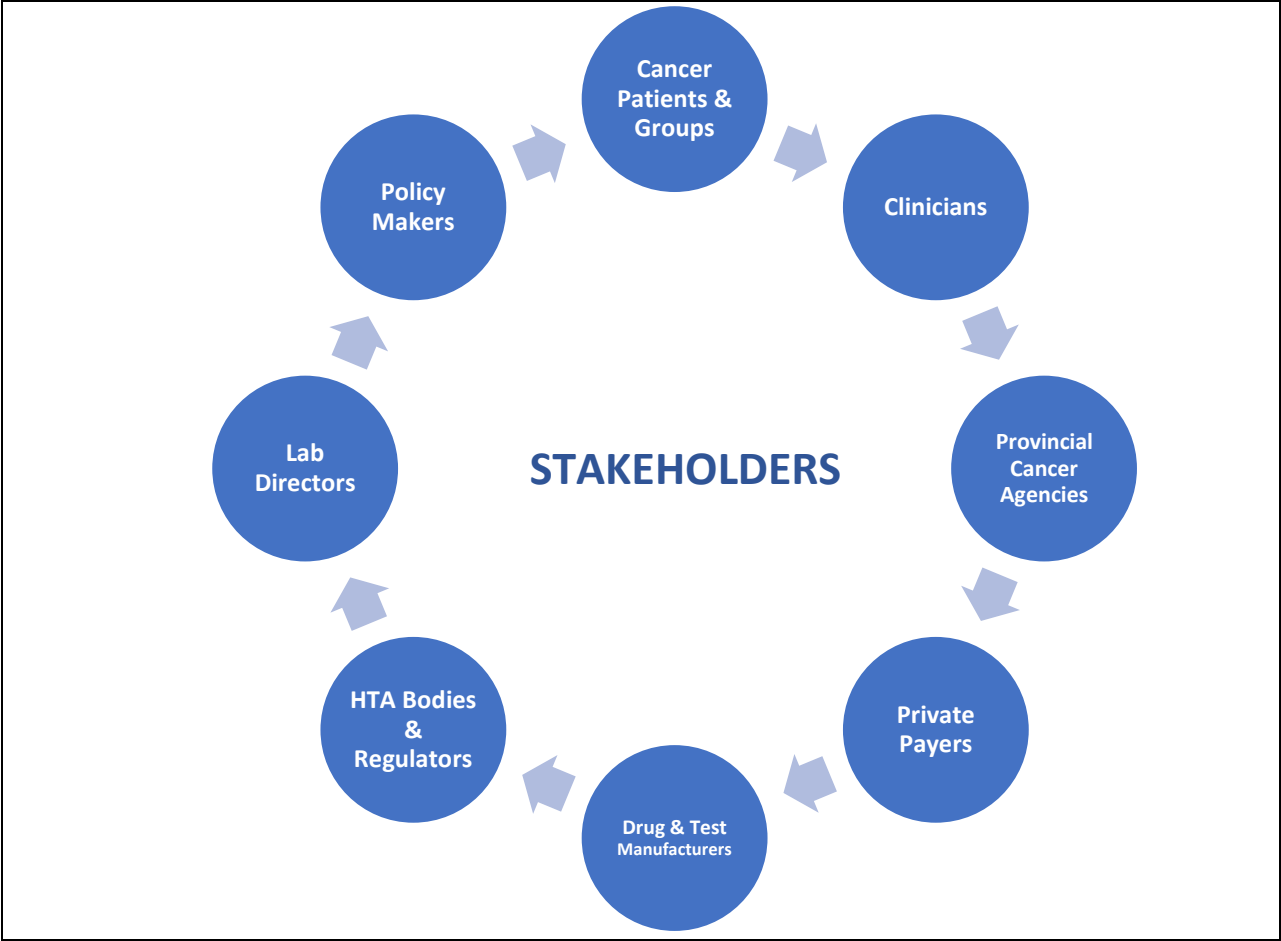
The objective of this report was to identify any challenges, barriers or gaps in the implementation or access to companion diagnostics in Canada through a literature review and series of stakeholder interviews. The concerns identified serve as opportunities to share value-based recommendations on how to potentially resolve some of those issues in a collaborative manner.

A limitation associated with the review is the low number of stakeholder interviews secured. Of the 26 stakeholders approached across Canada for requested telephone interviews, only eight were eager to participate and provide input. In addition, when seeking to obtain feedback on NGS testing from interviewed cancer patients, tumour type distribution was skewed, for there were an inordinate number of colorectal cancer patients interviewed in comparison to other tumour type patients, and patients interviewed were generally located in Ontario and Nova Scotia. While every effort was made to conduct an efficient and thorough literature review of the Canadian landscape, the review was not exhaustive. Nor was an international HTA review included for comparative purposes (i.e. U.S. Europe, Australia).

For those immersed in the oncology space, it is more than apparent that the development of therapeutic products that are paired with diagnostic tests is becoming increasingly common. Currently available companion diagnostic tests aim to detect a single biomarker to genetic variance in a single gene; but whole genome sequencing and genomic profiling of tumours is now possible, and patients are requesting NGS testing of their tumours.

For patients, the ability to access these technologies can directly impact their treatment options and health outcomes. Where a patient resides in Canada should not dictate access. Instead, patients should be able to access companion diagnostics regardless of their postal code. And equitable patient access across Canada must be an important objective of companion diagnostics policy for all stakeholders. The review, however, revealed challenges that threaten widespread patient access across the country – not the least of which is the lack of standardized testing across Canada, limited budgets and resources, funding frameworks, and the decentralized nature of healthcare decision-making throughout Canada. With the introduction of Next Generation Sequencing Testing, thoughtful consideration must also be given to its clinical utility to improve patient outcomes.

This review should serve as the impetus for action to be taken in Canada: to bring together the various stakeholders in Canada to promote a collaborative movement in the advancement of companion diagnostics in so far as how they are regulated, evaluated, funded, implemented and ultimately accessed by patients. Invited Stakeholders would consist of the following critically important core participants:



**Figure 16: A Call to Action – Inviting Stakeholders to Provide Real, Meaningful Change**

This report encourages an ongoing, considerate, and expert discussion of the concerns identified in this paper, beginning with the scheduling of a roundtable meeting of interested stakeholders. Stakeholders who are eager to work together toward reform will provide real value and change in patient management. Timely and equitable access to companion diagnostics can impact patient outcomes and translate into improved healthcare: the companion diagnostic test is the key to not only identifying the right patient population but also to reaching as many patients as possible within that population. *“A platform approach to integrating multiple stakeholders will....prove that precision medicine is not a zero-sum game for stakeholders but, rather, an opportunity for shared gains.”<sup>2</sup>*

Interviewed stakeholders expressed their desire to continue to be engaged in this dialogue and wished to be part of this ongoing initiative, which would ultimately lead to equitable and greater patient access across Canada. Their hope was that more awareness, education and adoption would be generated in respect of NGS Testing to advance its clinical utility in the management of metastatic cancer. **Brandon**

**Levac** from Bayer Canada referenced NGS testing three times when replying to Question #1, #2, and #5. Appearing below are the respective replies:

1. *“Efficiencies with moving to **NGS** for multiple targets vs. conducting individual sequential tests.”*
2. *“Move to **NGS** based screening for efficiency.”*
5. *“Pairing of 1 test: 1 drug is an outdated model with **NGS**. How do you assign costs by drug when a single panel may screen for dozens of biomarkers and many associated treatments? Costs also decrease with higher adoption of **NGS** and increased test volumes – significant difficulty with adapting to cost changes for tests on an ongoing basis, unlike drugs.”*

As markers become more numerous and better understood, they will continue to be helpful in directing the appropriate use of therapeutics for cancer patient populations. Cancer patients desperately seek the holy grail of bioinformatics that will permit them to proceed to treatments that will improve their health outcomes. It is the responsibility of all stakeholders to help patients with their quest to gain access to the diagnostics that have the potential to make precision cancer care more effective and highly accessible across the country.

## APPENDIX A: STAKEHOLDER INTERVIEW QUESTIONS

1. In your view, are there any barriers, challenges or gaps related to implementing or accessing companion diagnostics in Canada in so far as:
  - (i) Regulatory Approval
  - (ii) Evaluation of the companion diagnostic (HTA)
  - (iii) Reimbursement of the companion diagnostic
  - (iv) Laboratory Operations
2. In your opinion are there any solutions in helping to address any or all of the challenges related to implementing or accessing companion diagnostics in Canada? If so, what are they?
3. A. Co-development of companion diagnostics occurs when a biomarker is identified, validated and utilized in a clinical trial alongside the investigational drug.  
B. Would you recommend co-development of the test and drug? Why or why not?  
C. Do you see challenges or barriers in the co-development of the test and drug? If so, what are they?
4. A. Do you believe the performance of the test should be closely tied to the performance of the associated drug? And that this relationship is essential for determining the safety and effectiveness of the products for patient use?
5. A. Would you support combining the cost of the test and the drug as a solution and step forward in the reimbursement decision process at the provincial jurisdictional level?  
B. Would you support accelerating the regulatory approval process?
6. Do you believe standardized methods for determining clinical utility and reimbursement for diagnostic tests are lacking in Canada? If so, why?
7. Who would you consider to be the various stakeholders impacted both negatively and positively from the implementation or lack of implementation of companion diagnostics in Canada?
8. A. Can oncology patients provide meaningful and compelling input on companion diagnostics and how they stand to benefit from accessing a companion diagnostic?  
B. If so, at what level and through which process (format) would their input be provided?

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#### Image Sources:

**Figure 1: Precision Medicine In The Treatment of Cancer**

Understanding Precision Medicine in Cancer Treatment:

<https://www.slideshare.net/jackiemanthorne/new-diagnostics-guiding-oncology-treatment-decisions>

**Figure 2: The Promise of Precision Medicine**

Understanding Precision Medicine in Cancer Treatment:

<https://www.slideshare.net/jackiemanthorne/new-diagnostics-guiding-oncology-treatment-decisions>

**Figure 3: Precision Medicine – Targeted Therapy and its Associated Companion Diagnostic**

Understanding Precision Medicine in Cancer Treatment:

<https://www.slideshare.net/jackiemanthorne/new-diagnostics-guiding-oncology-treatment-decisions>

**Figure 6: Understanding Precision Medicine in Cancer Treatment**

Understanding Precision Medicine in Cancer Treatment:

<https://www.slideshare.net/jackiemanthorne/new-diagnostics-guiding-oncology-treatment-decisions>

**Figure 7: Six Common Barriers to the Adoption of Companion Diagnostic Tests**

Keeling, Peter, et al., Challenges in the clinical implementation of precision medicine companion diagnostics. Expert Review of molecular diagnostics. 20:6, 593-599,

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**Figure 10: AHS - Innovation to Action Lifecycle**

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**Figure 11: Interprovincial Variability Across Canada Regarding Quality Standards of Lab Tests**  
**Understanding Precision Medicine in Cancer Treatment:**

<https://www.slideshare.net/jackiemanthorne/new-diagnostics-guiding-oncology-treatment-decisions>

**Figure 12: Genomic Testing Guiding Treatment Decision Making in Oncology**  
**Review of HTA frameworks and Decisions for Next-Generation Sequencing in Precision Oncology**

<https://www.xcenda.com/insights/htaq-summer-2019-hta-decision-for-next-generation-sequencing>

**Figure 13: Benefits & Challenges of Next Generation Sequencing for Clinical Diagnostics and Biomarker Testing in Oncology.**

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