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Companion Diagnostics (CDx) Policy Discussion Paper

Issues, Gaps and Opportunities for Change in Canada

This report was drafted in support of the stakeholder roundtable at the Summit for Cancer Immunotherapy 2017 for BioCanRx by Katherine Bonter, Director of Intellectual Property at Clementia Pharmaceuticals, Rachael Manion, Senior Associate & Director of Research at 3Sixty Public Affairs and Johanne Chambers, President of 3Sixty Public Affairs.

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INTRODUCTION

The era of precision therapeutics has arrived and has had its greatest impacts in oncology. As cancer research uncovers a multitude of nuances in tumours, patients, their care teams and healthcare systems increasingly rely on diagnostic tests that will help determine the effectiveness of a specific treatment for a specific patient. A diagnostic test relied on to guide treatment decisions – in particular, to provide information that enables the care team to deliver more precise, safer and more effective use of a specific drug – is often called a companion diagnostic. This term describes the fact that the test is tailored to provide information relevant to the use of a corresponding drug.

While the drug development, evaluation and funding pathways in cancer are robust, similar systems for companion diagnostics have not kept pace. Health systems are developing a range of policies and processes to support the development and adoption of companion diagnostics and other precision cancer medicine tools in Canada.

To provide guidance to health system policy makers, BioCanRx hosted a roundtable in 2016 to discuss the particular challenges presented by molecular diagnostics for cancer treatments. Given the growing number of medicines with companion diagnostics and the increasing reliance on companion diagnostics within the immuno-oncology sphere, BioCanRx developed this discussion guide to form the basis of a second roundtable discussion on molecular diagnostics at the Summit for Cancer Immunotherapy on June 28, 2017.

This paper sets out background information on companion diagnostics and key gaps and challenges related to the adoption of these technologies in health systems throughout Canada, with a focus on health system operations and policy that influence the evaluation, funding and delivery of companion diagnostics as a type of personalized or precision medicine. The analysis is based on a literature review conducted by BioCanRx about policy challenges and proposed solutions to support the adoption of companion diagnostics in the Canadian healthcare system. A series of questions to help guide the discussion at the 2017 Summit is included below. This discussion will support further development of a white paper on the policy challenges posed by companion diagnostics and the solutions proposed by health system stakeholders to improve patient access to these technologies.

CONTEXT

Companion diagnostics are a form of precision medicine used to help a patient's care team determine the most appropriate and optimal use of a specific treatment. More specifically, companion diagnostics are tests developed to detect a particular biomarker in a patient that is essential to guiding the use of the corresponding drug to treat the patient. Such diagnostic tests include molecular diagnostics that provide genetic information, as well as tests to detect proteins, metabolites, essential elements, tracers, imaging tools and other biomarkers.

In its analysis of *Pharmaceuticals Requiring Companion Diagnostics*, the Canadian Agency for Drugs and Technologies in Health (CADTH) stratified companion diagnostics based on the information that they identify, specifically:¹

- Tests that inform the prognosis for a patient, i.e., whether they are genetically predisposed to a particular disease (**prognostic biomarker**)
- Tests that predict how treatment would proceed or have a sensitivity to a drug or a group of patients who would benefit from treatment with a drug (**predictive biomarker**)
- Tests that determine the specific dosage of a drug that a patient would receive (**pharmacodynamics biomarker**)

For the purposes of this report, a companion diagnostic is a diagnostic test that is required by the regulator as a condition of using the drug (e.g., is included in the drug's product monograph by Health Canada).

The development of companion diagnostics and related targeted treatments have increased in recent years, as the understanding of the molecular drivers of disease has grown and treatments that target these processes have shown improved health outcomes. As of June 2016, 19 companion diagnostics had received regulatory authorization from Health Canada, according to CADTH's report *Pharmaceuticals Requiring Companion Diagnostics*.² For a description of these companion diagnostics, see Appendix 1.

Some companion diagnostics are considered to be medical devices (*in vitro* diagnostic devices) and / or laboratory tests. In Canada, drugs, medical devices, and laboratory tests all enter the health system through different pathways without much formal coordination between them. Precision therapeutics for cancer, such as medicines that rely on a companion diagnostic, present 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.

It has been suggested that in Canada, "the rate of scientific discovery is outpacing system capacity and infrastructure to effectively accommodate the adoption precision medicine in clinical practice and public policy".³ In particular, three key themes in terms of the policy challenges presented by companion diagnostics in Canada were identified at a stakeholder meeting led by CADTH in 2014: (1) financial

¹ CADTH. (2014; partially updated 2016). *Environmental Scan, Pharmaceuticals Requiring Companion Diagnostics*, online: https://www.cadth.ca/sites/default/files/pdf/ES0301_Drugs_with_cDx.pdf

² *Ibid.*

³ Roche Consultancy Meeting on Personalized Medicine, June 2016. (2016)

capacity; (2) evidentiary requirements; and (3) legal, social and innovation issues.⁴ These factors and dynamics are inter-related and complex. However, it is necessary to understand them better to optimize the benefits that can be derived from currently available and future innovations.

Firstly, the implementation of new drugs or diagnostic tests is influenced by the financial capacity of the healthcare system or specific healthcare institution (e.g., hospital) that funds the drug or diagnostic test.

Secondly, health system decision-makers require different types of evidence in order to determine whether or how to make the technologies available to patients. To satisfy these requirements, innovators demonstrate the clinical or pharmacoeconomic value of the innovation they would like to see funded.

Thirdly, there are legal, social and innovation implications of the outcomes of these processes: which innovations are implemented or adopted by the healthcare system (or specific healthcare institutions) how this process unfolds. Ideally, the implementation process should be designed to optimize the health and social benefits that can be achieved through the spending of our healthcare dollars.

From an innovation perspective, the successful adoption of specific technologies in the health system – such as drugs with companion diagnostics – holds implications for innovators and the process of innovation. Innovators will continue to invest in those technologies that are successfully adopted and funded in a way that sufficiently rewards their efforts. As well, where certain evidence is required to demonstrate value and support health system adoption, innovators will prefer to design studies that elicit this type of evidence. The type of evidence sought by health system decision makers will also influence the costs and risks associated with innovating.

For patients, the ability to access these technologies can directly impact their treatment options and health outcomes. Patient interests have been acknowledged as a central concern in addressing the issues presented by companion diagnostics: "patient interests remain paramount in all health system reform efforts, and [...] the patient [should be] represented in the redress of the many barriers to precision therapeutics implementation".⁵

Equitable patient access across the country should be an objective of companion diagnostics policy in Canada.⁶ However, the decentralized nature of health system decision-making throughout the country, along with limited budgets and resources for adopting healthcare innovations collectively challenge this objective.⁷ In addition, the evidence requirements for successful evaluation and funding of companion diagnostics in Canada are not clear. Some have suggested that a lack of real-world evidence hinders decision-making and optimal spending,⁸ and even that this type of evidence could be "critical for

⁴ CADTH. (2015). *Meeting Summary, Health Technology Strategy Policy Forum Wider Table on Personalized Medicine*. CADTH. Retrieved from https://www.cadth.ca/sites/default/files/policy_forum_section/Wider_Table_Mtg_Summary_Feb_26-27_2015_Final_May_2015.pdf.

⁵ Slater, J., Shields, L., Racette, R. J., Juzwishin, D., & Coppes, M. (2015). The emergence of precision therapeutics: New challenges and opportunities for Canada's health leaders. *Healthcare Management Forum*, 28(6 Suppl), S33–S39. <https://doi.org/10.1177/0840470415604771>.

⁶ CADTH. (2015).

⁷ Roche Consultancy Meeting on Personalized Medicine. (2016); Slater, J., Shields, L., et al. (2015); CADTH. (2014; partially updated 2016); MEDAC Laboratory Medicine Stakeholders. (2015). *Laboratory medicine: A strategic call to action*. Report from strategy meetings, October 2, 2014 and June 12, 2015 (Report from Strategy Meetings).

⁸ Roche Consultancy Meeting on Personalized Medicine. (2016); Slater, J., Shields, L., et al. (2015).

clinician, payer, and public confidence”.⁹ At the same time, CADTH has noted that “[i]ncreasing demands are being placed on manufacturers to establish the cost-effectiveness of their products for the allocation of funds”.¹⁰ Evolving policy in this area must be clarified as soon as possible to enable innovators to adapt and ensure that beneficial innovations can be made available to Canadian patients.

This report sets out a number of policy gaps that have been identified in terms of how companion diagnostics are regulated, evaluated and funded and articulates recommendations to improve the adoption of companion diagnostics in Canada.

⁹ Slater, J., Shields, L., *et al.* (2015).

¹⁰ CADTH. (2014; partially updated 2016).

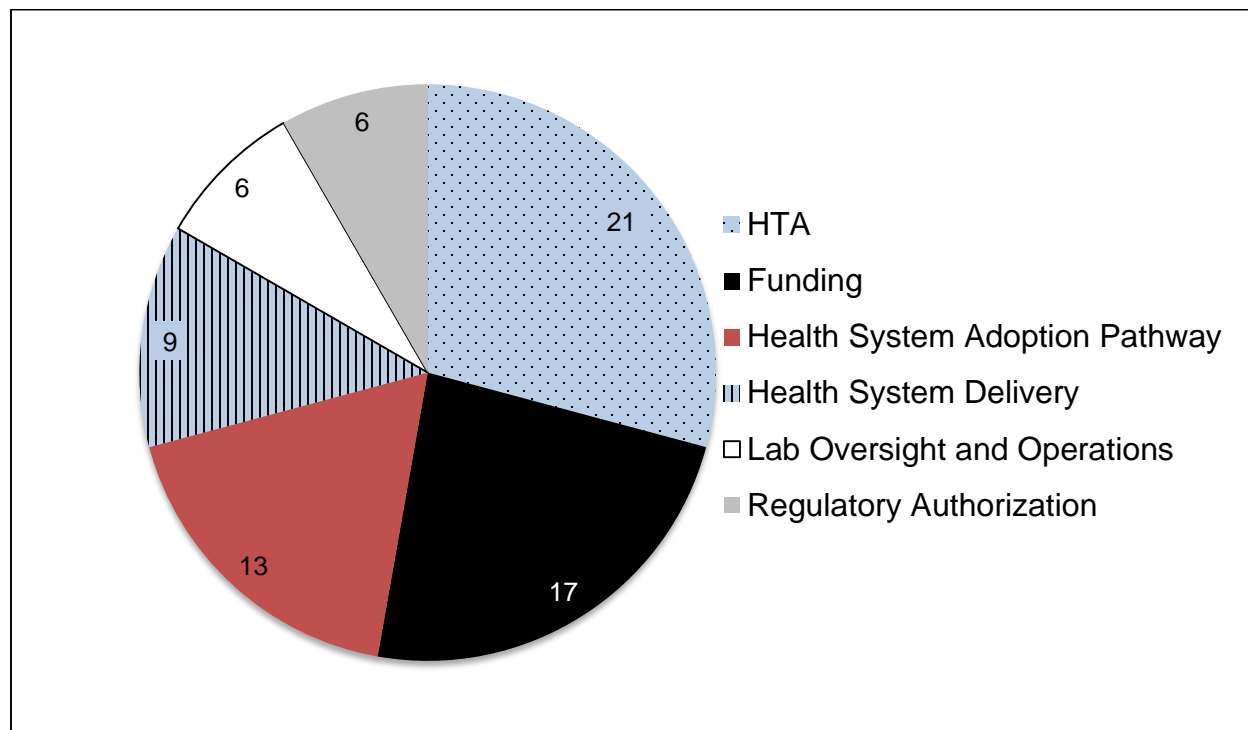
HEALTH SYSTEM ADOPTION OF CDx: GAPS AND CHALLENGES

In order to identify key challenges and recommendations related to different steps in the pathway to health system adoption, a literature review was conducted of articles published between 2012-16 that express Canadian stakeholder opinions on policy or operational problems related to Canadian healthcare system evaluation, funding and delivery of companion diagnostic tests. For methodology notes, please see Appendix 2.

This analysis uncovered broad representation from a variety of stakeholders. Seventy-two different Canadian stakeholder organizations are represented in the set of documents reviewed. There was also a range of representation from different organizations in the public and private sectors (for further details, see Table 9 in Appendix 2).

The challenges identified and recommendations made by the authors reviewed were most frequently associated with health technology assessment (HTA), followed by funding, the health system adoption pathway in general and health system delivery. Based on the number of times the issues were identified in the literature reviewed (see Table 1 below), challenges posed by the current approaches to HTA and funding of companion diagnostics appear to be the most pressing concerns for stakeholders.

Table 1. Topic Areas Identified Through Literature Review



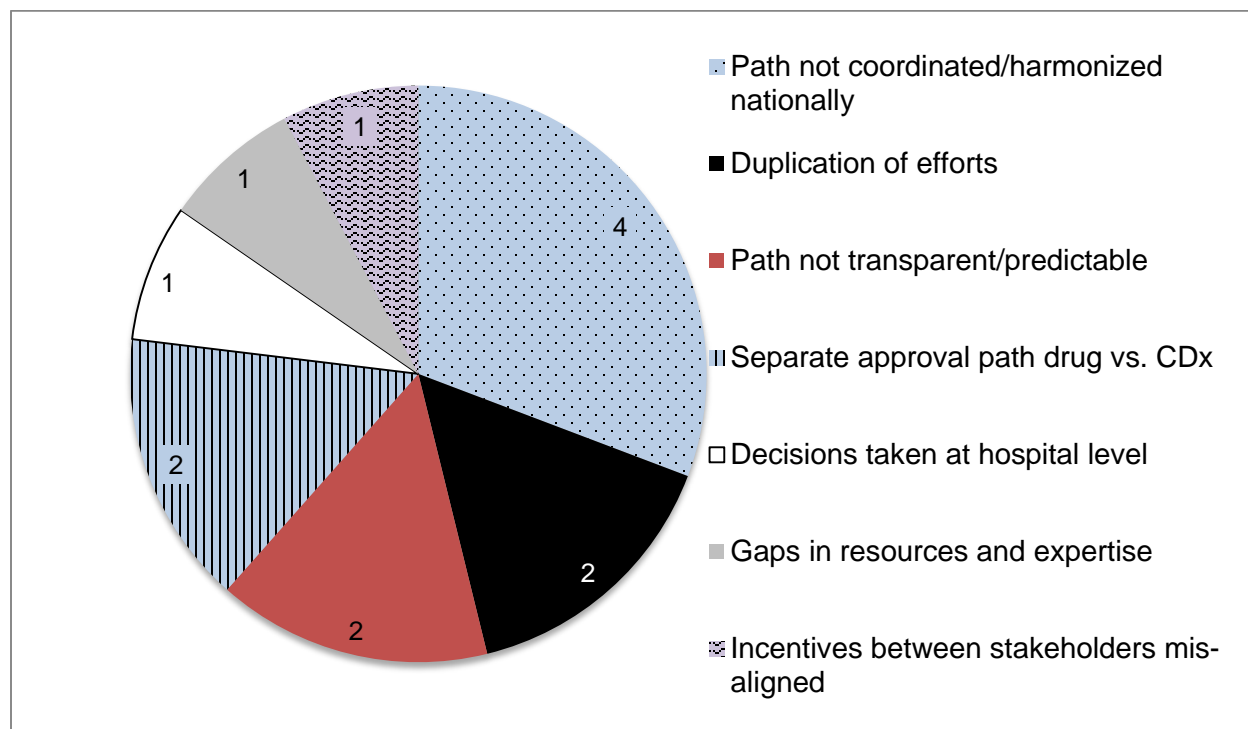
1. Health System Adoption Pathway

In Canada, drugs are made available for patients’ treatment through a different pathway than medical devices (including *in vitro* diagnostic devices) and laboratory services. The stages that each category of health technology follows are not the same. Importantly, there is no formal coordination across all of these pathways, which can result in a drug being available prior to its companion diagnostic, or uneven access to the drug and / or companion diagnostic from jurisdiction to jurisdiction.

Challenges

In several of the documents published on the issue of companion diagnostics policy in Canada, stakeholders identified seven types of challenges presented by the current health system adoption pathway for drugs and their companion diagnostics. Challenges posed by the current health system adoption pathway reflect multiple steps followed by drugs and companion diagnostics from regulatory authorization to patient access (see Table 2 below).

Table 2. Challenges Posed by the Current Health System Adoption Pathway



- The path is not harmonized nationally, resulting in inter-provincial differences.** Beginning with the regulatory process conducted at the federal level by Health Canada, through to decisions about which drugs and companion diagnostics to reimburse at the provincial level, there is often a “misalignment and lack of coordination” at various levels of policy making.¹¹ Regulation of *in vitro* diagnostic tests, conducted by Health Canada, and the practice of performing laboratory-developed tests, regulated provincially, is not well-coordinated, creating potential gaps in standards and

¹¹ Slater, J., Shields, L., *et al.* (2015).

practices that result in different levels of access to such tests across the country.¹² The reimbursement processes and practices used by jurisdictions vary and are often inconsistent.¹³ The organizational structure of healthcare systems across the separate program areas, e.g., pharmaceuticals, hospitals, and laboratory services, creates a barrier to more consistent practices as each broad program area has its own budget and decision-makers who determine the basket of services that the budget will support, including drugs and companion diagnostics.¹⁴

- **Duplication of efforts nationally and provincially.** Across the health system, the lack of coordination and streamlined system for health system adoption of drugs and their companion diagnostics creates inefficiencies and duplication.¹⁵ Of particular relevance to the oncology context, where decisions regarding whether to reimburse an oncology drug and its companion diagnostic are made by hospitals, the lack of a consistent approach among institutions can result in duplication of efforts and is a barrier to the creation of standardized policies for each jurisdiction.¹⁶
- **The path is not clear or predictable.** In light of the different approaches to regulating and reimbursing companion diagnostics and the fast pace of technological evolution in this area, there is an absence of clear health system adoption pathways throughout the country.¹⁷ The policies employed by various health systems – and related language – are inconsistent.¹⁸ In particular, the documents reviewed noted inconsistent processes, criteria, policies and language. For innovators, this is an important issue: knowing what evidence will be required for successful adoption of these technologies creates uncertainty and exacerbates risk. For healthcare decision makers, not having clear criteria and practices further complicates decision-making.
- **Separate health system adoption path for drug and its CDx.** There is no process that will accommodate the review of both the drug and its companion diagnostic together.¹⁹ From the perspective of manufacturers of the drug and companion diagnostic, the existence of separate pathways leaves them without the ability to engage with both sets of decision-makers together.²⁰
- **Decisions vary with individual hospitals.** Hospitals are under pressure to make new companion diagnostics available with their corresponding drugs but may not receive extra funding to do so.²¹
- **Gaps in resources and expertise needed.** At each stage of the pathway, from regulatory authorization to health system adoption, relevant expertise and supportive resources are needed. However, there are multiple gaps in such expertise and resources.²²

¹² Gibson, S., & Lemmens, T. (2015). The Promise and Peril of Adapting the Regulatory System to the Pharmacogenomic Context. *McGill Journal of Law and Health*, 8(2).

¹³ Roche Consultancy Meeting on Personalized Medicine. (2016).

¹⁴ Manion, R. & Dempster, B. (2016). Companion Diagnostics for Innovative Pharmaceuticals: Facilitators or Obstacles to Market Access? *Provincial Reimbursement Advisor*, 19(3), 1–106.

¹⁵ Roche Consultancy Meeting on Personalized Medicine. (2016).

¹⁶ CADTH. (2014).

¹⁷ Manion, R. & Dempster, B. (2016).

¹⁸ Roche Consultancy Meeting on Personalized Medicine, June 2016. (2016).

¹⁹ CADTH. (2014). *Environmental Scan, Pharmaceuticals Requiring Companion Diagnostics* (CADTH Environmental Scan). Retrieved from

http://www.cadth.ca/media/pdf/CADTH%20Environmental%20Scan_%20Companion%20Diagnostics_25June2014_Ver%204.0_For%20Stakeholder%20Feedback.pdf

²⁰ Manion, R. & Dempster, B. (2016).

²¹ CADTH. (2014).

- **Stakeholder incentives are not aligned.** Several stakeholders are involved in developing companion diagnostic technologies, making decisions about reimbursement, implementing the technologies in the health system and providing care to patients, each of which has their own incentives for decision-making. Companion diagnostics policy should include incentives to align these stakeholders.²³

Recommendations

Stakeholders have advanced several specific approaches to address the challenges that are identified above.

- **Engage and improve coordination / alignment across all stakeholders.** Several of the challenges raised are issues that cross provinces, organizations and functions fulfilled by different stakeholders. Addressing these challenges will likely require multi-stakeholder coordination and joint efforts. Among the recommendations put forward to address these challenges, multiple stakeholders identified the need to engage stakeholders to better align incentives and improve communication among industry, payers, regulators, health technology assessors and providers.²⁴ Early dialogue during the development of the technology was seen as key to creating better alignment and coordination among different stakeholders.²⁵ As well, options should be explored that support payers through a more predictable and coordinated approach to evidentiary requirements and processes among regulators and HTA bodies.²⁶
- **Create an advisory body to address patchwork approach to health system adoption of companion diagnostics.** Better coordination and alignment across jurisdictional boundaries was also recommended²⁷ and could be achieved through the creation of a multi-stakeholder advisory body to advise governments in Canada.²⁸
- **Provide consistent laboratory oversight in Canada.** A national body that has the authority to promote good laboratory practices and sanction laboratories has also been recommended.²⁹
- **Provide the health system with the tools to eliminate older technologies and better facilitate the uptake of new technologies.** In addition to improving the ability to introduce companion diagnostics, health systems should have greater tools to de-list or curtail access to older

²² Slater, J., Shields, L., *et al.* (2015).

²³ Institute of Health Economics (IHE). (2012). *Personalized Medicine - Policy Gaps and System Readiness* (p. 13). Alberta Canada.

²⁴ McCabe, C., & Husereau, D. (2014). *Personalized Medicine and Health Care Policy: From Science to Value*. Retrieved from http://www.genomecanada.ca/medias/pdf/en/PersonalizedMedecine_Policy-Directions-Brief.pdf

²⁵ Garfield, S., Polisena, J., Spinner, D. S., Postulka, A., Lu, C. Y., Tiwana, S. K., Faulkner, E., Poullos, N., Zah, V., Longacre, M. (2016). Health Technology Assessment for Molecular Diagnostics: Practices, Challenges, and Recommendations from the Medical Devices and Diagnostics Special Interest Group. *Value in Health*, 19(5), 577–587. <https://doi.org/10.1016/j.jval.2016.02.012>

²⁶ McCabe, C., & Husereau, D. (2014).

²⁷ Slater, J., Shields, L., *et al.* (2015).

²⁸ Roche Consultancy Meeting on Personalized Medicine. (2016).

²⁹ Butts, C., Kamel-Reid, S., Batist, G., Chia, S., Blanke, C., Moore, M., Sawyer, M.B., Desjardins, C., Dubois, A., Pun, J., Bonter, K., Ashbury, F. D. (2013). Benefits, issues, and recommendations for personalized medicine in oncology in Canada. *Current Oncology*, 20(5), 475. <https://doi.org/10.3747/co.20.1253>

technologies, which was seen as facilitating a better allocation of finite resources towards more advanced technologies.³⁰

2. 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 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 manufacturer, 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 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 or system (considered a medical device) for review, each is subject to different regulations and reviewed by different directorates within Health Canada. Where 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.

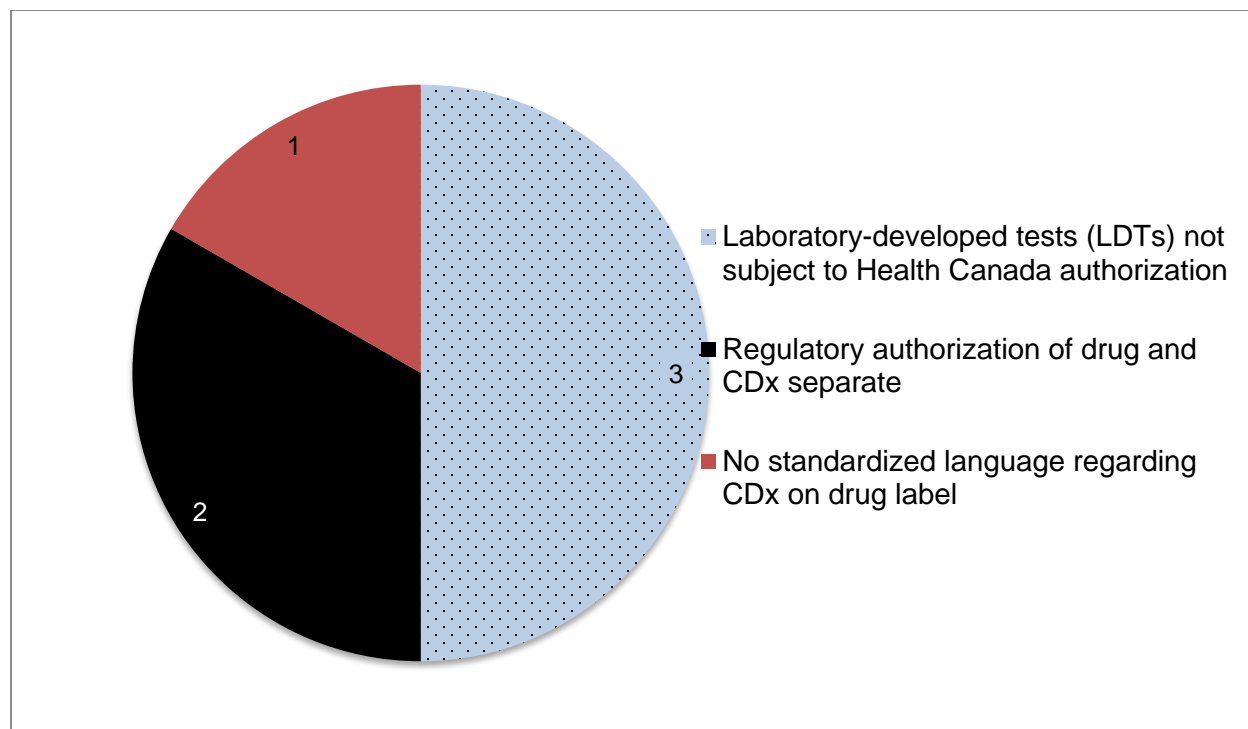
Laboratory tests that are developed in-house by laboratories may be used as companion diagnostics but are not regulated by Health Canada as medical devices. Furthermore, there is no regulation of laboratory services at the federal or national level, although laboratories may wish to be accredited against extensive standards established by Accreditation Canada.

Challenges

As an area of concern within the health system adoption pathway, regulatory authorization overall received less attention from stakeholders. Within the seven documents reviewed that articulated challenges posed by the current approach to regulating drugs and their companion diagnostics, stakeholders identified three key issues (see Table 3 below).

³⁰ CADTH. (2015).

Table 3. Challenges Posed by the Current Approach to Regulatory Authorization



- **Laboratory-developed tests are not subject to Health Canada authorization.** As mentioned above, laboratory developed tests (LDTs) are not required to be approved by Health Canada (with the exception of diagnostic devices that may be used as part of an LDT). Health Canada regulates health products – services are regulated by provinces. Laboratory practices, which would encompass the in-house development of an LDT, differ across provinces. This issue received the lion’s share of stakeholder attention as a key challenge resulting from the regulatory authorization system.³¹
- **Drugs receive regulatory authorization separately from their companion diagnostics.** There is no formal process for Health Canada to review companion diagnostics as part of the review of their corresponding drug. The fact that they are seen as two separate products and not as a pairing sets the stage for separate treatment throughout the health system adoption pathway.³²
- **Drug labels do not have standardized language regarding their companion diagnostics.** A drug’s reliance on a companion diagnostic is not uniformly captured in the product monograph for the drug. In fact, “information related to diagnostic testing may be included in different sections of the monograph and under different titles”.³³

³¹ CADTH. (2014); OPMN. (2014). *Evaluating our Current Health Technology Assessment Capabilities in Light of Personalized Medicine Technologies*. Ontario Personalized Medicine Network. Retrieved from <http://www.ontariogenomics.ca/sites/default/files/OPMN%20Subcommittee%20Report%20Post-Market%20Framework.pdf>; Canadian Cancer Research Alliance, & Robbins, S. (2015). *Molecular Diagnosis Hubs Workshop: In Support of the CCRA Target 2020 Framework*

³² Manion, R., & Dempster, B. (2016); McCabe, C., & Huserau, D. (2014).

³³ Gibson, S., & Lemmens, T. (2015).

Recommendations

Robust regulatory processes help support the benefits of a diagnostic device that has demonstrated that it is of high quality. In particular, regulatory authorization of a companion diagnostic can give rise to better quality control, harmonization across the provinces, faster validation and delivery across the country, a more straightforward assessment of the value of a particular drug and its companion diagnostic as well as value-based pricing and reimbursement approaches for the companion diagnostic. These benefits encourage prudent healthcare spending and better health outcomes for patients. Stakeholders in the documents reviewed identified two specific recommendations regarding regulatory oversight of companion diagnostics.

- **Improve quality assurance of diagnostic tests.** An “effective framework for clinical laboratory operations, medical testing and diagnostic devices” could reduce the variability in diagnostic testing across Canada.³⁴
- **Greater emphasis on clinical utility by regulators.** In order to identify the most promising personalized medicine innovations, the regulation of companion diagnostics should include a greater focus on the clinical utility of the technologies.³⁵

3. Health Technology Assessment

In order for public drug plans to reimburse a drug, it must undergo a health technology assessment (HTA) to determine its clinical effectiveness and cost-effectiveness in the context of other available treatments. At a pan-Canadian level, CADTH conducts HTAs for oncology drugs through its pan-Canadian Oncology Drug Review (pCODR) program, which ends in a reimbursement recommendation to public payers based on its assessment of a drug’s clinical and cost-effectiveness. In addition to specifying whether payers should reimburse the drug, the recommendation may also include terms and conditions (e.g., a reduction in price or continued study and reporting of results).

While CADTH only reviews some medical devices, its work in this area is increasing, and more attention is being given to laboratory and imaging services through its Rapid Review and medical devices evaluation initiatives.

In fact, CADTH recently announced the HTA process it will implement in October 2017 for drugs with their companion diagnostics.³⁶ While the HTA review process for companion diagnostics that was initially proposed by CADTH in the context of stakeholder discussions in November 2016 included an independent assessment of the diagnostic test, the process that will be implemented will not review companion diagnostics associated with a drug. Rather, CADTH will focus on evidence relating to the impact of biomarker testing for a specific drug: “CADTH’s overarching objective is to explicitly and consistently investigate factors relevant to any required biomarker testing that would inform the implementation of associated drugs under review” through CADTH’s programs, including pCODR. Manufacturers (or others seeking funding of a companion diagnostic) must still provide specific clinical information and pharmacoeconomic information related to the companion diagnostics if Health Canada requires biomarker testing to guide patient treatment:

³⁴ CADTH. (2014).

³⁵ Institute of Health Economics (IHE). (2012).

³⁶ CADTH. (2017). *Health Technology Assessment of Drugs With Companion Diagnostics at CADTH*. Retrieved from https://cadth.ca/sites/default/files/cdr/cdr-pdf/CDx_Process.pdf.

- **Clinical information:** Evidence that “highlight[s] the clinical utility of the companion diagnostics under review” and
- **Pharmacoeconomic information:** Information about the “costs and consequences” of companion diagnostics (such a false positives or negatives and how frequently they occur).

In its review of companion diagnostics, CADTH will receive additional input:

- Experts in pathology and/or laboratory testing,
- Patient input about “their expectations and/or experiences with any required biomarker testing” for the drug under review, and
- Jurisdictions’ “insights into the enablers and barriers related to any required biomarker testing”.

The final recommendation from CADTH about a drug-companion diagnostic pair will not refer to any specific laboratory test. Using the same framework as it uses for drugs, CADTH reviewers may include clinical criteria or conditions related to the companion diagnostic.

Not all jurisdictions rely exclusively on CADTH’s HTA processes. In addition to the pan-Canadian HTA processes conducted by CADTH, individual jurisdictions have their own entity (e.g., Quebec’s Institut national d’excellence en santé et en services sociaux or INESSS) or directorate within the health ministry to conduct HTAs and may also conduct their own HTA of a drug and/or companion diagnostic. However, as CADTH has broadened its scope, the trend has increasingly been to rely on CADTH for these assessments.

Challenges

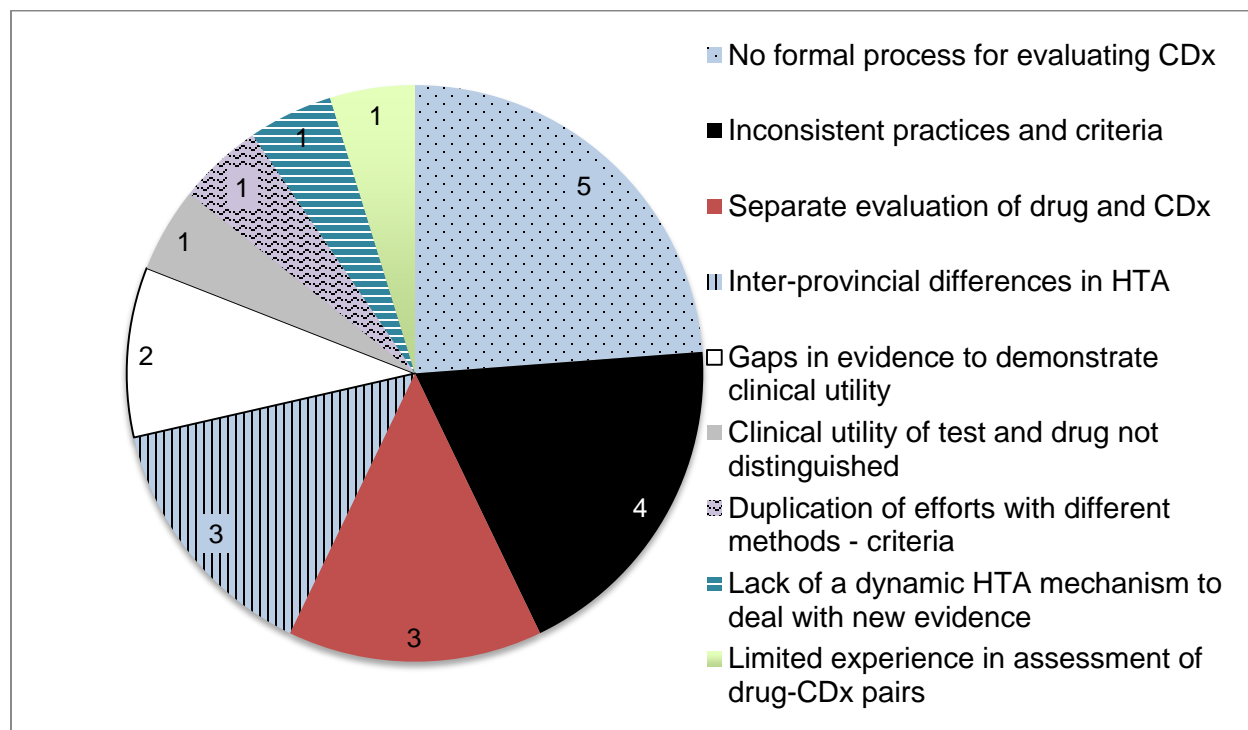
Health technology assessment policy in Canada has been slow to respond to the unique needs of companion diagnostics. In the absence of a pan-Canadian HTA process that evaluates these technologies appropriately, provincial ministries of health have responded on a largely ad hoc basis, creating gaps and inconsistencies in how such technologies are evaluated in Canada. This poses follow-on challenges for innovators and health system decision-makers who rely on such analyses, resulting in a patchwork of patient access to these technologies.

Stakeholder reviews of the challenges posed by HTA centred around two main themes. Firstly, stakeholders identified several challenges posed by the absence of a consistent approach to evaluating drugs and their companion diagnostics together across the country. Secondly, the lack of clarity around the evidential requirements to demonstrate clinical utility of companion diagnostics also resulted in uncertainty for innovators and health system decision-makers, resulting in compromised access to these technologies for patients (see Table 4 below).

It should be noted that stakeholders’ views outlined below were provided prior to CADTH’s introduction of its new HTA process for drugs with companion diagnostics in early June 2017. Some of the gaps and recommendations identified below will therefore have to be assessed with this new HTA process in mind. However, some of the issues raised by stakeholders still remain relevant, as CADTH’s new process is focused on the evaluation of the drug that has a companion diagnostic. In other words, there may still be gaps in the evaluation of a companion diagnostic, which will pose challenges for reimbursement and health system adoption of companion diagnostics. As well, specific criteria regarding the evidence required to demonstrate the clinical utility of companion diagnostics remain unclear at this early stage

of implementation. Finally, provinces (including Quebec) may still rely on their own HTA process, which does may include a formal process for evaluating a companion diagnostic with the associated drug.

Table 4. Challenges Posed by the Current Approach to HTA



- Lack of a formal process for evaluating companion diagnostics.** The (previous) absence of a formal process potentially resulted in “politicizing decisions or failing to consider cost offsets beyond individual silo budgets”. Funding decisions are made by individual ministries of health and the absence of a national process left many without any standardized review processes as well as “established mechanisms to implement test use”.³⁷ In particular, CADTH noted that “no specific reimbursement policies for companion drugs and associated diagnostics were identified from any of the provincial bodies” in its 2014 environmental scan (updated in 2016).³⁸ The Ontario Personalized Medicine Network highlighted the need to “develop approaches to reviewing clinical trial data where the trial included the use of a companion diagnostic”.³⁹
- Practices and criteria are inconsistent.** Related to the lack of a formal evaluation process, stakeholders cited inconsistent and problematic HTA practices and criteria.⁴⁰ Some noted a variation in HTA outcomes depending on the method used⁴¹ or the extent to which certain criteria are either absent or vague.⁴² In general, it was suggested that Canadian organizations do not provide clear

³⁷ Butts, C., Kamel-Reid, S., et al. (2013).

³⁸ CADTH. (2014).

³⁹ OPMN. (2014).

⁴⁰ Dawe, D. E. & Ellis, P. M. (2012). Challenges in Implementing Personalized Medicine for Lung Cancer within a National Healthcare System. *Journal of Personalized Medicine*, 2(3), 77–92. <https://doi.org/10.3390/jpm2030077>; Butts, C., Kamel-Reid, et al. (2013); Garfield, S., Polisen, J., et al. (2016); Roche Consultancy Meeting on Personalized Medicine. (2016).

⁴¹ Dawe, D. E. & Ellis, P. M. (2012).

⁴² Butts, C., Kamel-Reid, S., et al. (2013).

parameters of acceptability related clinical utility or economic impact.⁴³ Demonstrating clinical utility and cost-effectiveness of diagnostic tests was viewed as a potential barrier to implementing targeted therapies.⁴⁴

- **Evaluations of the companion diagnostic are conducted separately from the drug evaluation.** Related to the two challenges noted above, stakeholders also identified the fact that the evaluation of a companion diagnostic is conducted separately from that of the associated drug as problematic.⁴⁵ In addition, challenges associated with interpreting clinical evidence in a way that distinguishes between the “clinical utility of the test from that of the drug or the drug/test combination” was also acknowledged by stakeholders.⁴⁶
- **There are interprovincial differences in approaches to HTA.** Fragmentation of HTA nationally and interprovincial differences in approach were identified by stakeholders as a key challenge.⁴⁷ Even given overlapping or redundant HTA efforts nationally, it was noted that although “some provinces have evaluation-focused organizations and initiatives, those organizations are not mandated, nor do they communicate with each other to ensure equity and consistency across the country”.⁴⁸ This suggests that the expertise and efforts made in one part of the country are not sufficiently available for others in Canada to benefit from them, potentially hampering or slowing implementation nationally and compromising equitable patient access across the country.
- **There are gaps in evidence to demonstrate the clinical utility of a companion diagnostic.** Stakeholders noted that personalized medicine technologies are “by their very nature new and underpinned by limited and uncertain evidence compared to established technologies”.⁴⁹ This results in gaps in the evidence that is required to demonstrate clinical efficacy and related socioeconomic evaluations.⁵⁰
- **The clinical utility of the drug is not distinguished from that of its companion diagnostic.** Clinical utility of drugs is established using the gold standard of a randomized clinical trial (RCT). When the companion diagnostic is used in the RCT, this “complicates interpretation” of the results and makes it more challenging to distinguish between the clinical utility of the test and that of the test used in combination with the drug.⁵¹
- **Different standards and criteria result in duplication of efforts.** The use of different assessment methods and criteria results in a “considerable duplication of effort”.⁵²
- **There is a lack of a dynamic HTA mechanism to address new evidence.** Evaluations of drugs and their companion diagnostics must be able to respond to new evidence and scientific advances.⁵³

⁴³ Garfield, S., Polisena, J., *et al.* (2016).

⁴⁴ Dawe, D. E. & Ellis, P. M. (2012).

⁴⁵ CADTH. (2015); Manion, R. & Dempster, B. (2016); Slater, J., Shields, L., *et al.* (2015).

⁴⁶ OPMN. (2014).

⁴⁷ Slater, J., Shields, L., *et al.* (2015); Manion, R. & Dempster, B. (2016); Roche Consultancy Meeting on Personalized Medicine. (2016).

⁴⁸ Butts, C., Kamel-Reid, S., *et al.* (2013).

⁴⁹ McCabe, C. & Husereau, D. (2014).

⁵⁰ Slater, J., Shields, L., *et al.* (2015).

⁵¹ OPMN. (2014).

⁵² CADTH. (2015).

⁵³ Slater, J., Shields, L., *et al.* (2015).

- **Limited experience in the assessment of drug-companion diagnostic pairs.** Stakeholders have identified the “limited guidance and experience in health economic analyses” for the assessment of drugs and their companion diagnostics as a challenge to improving HTA of these technologies.⁵⁴

Recommendations

Stakeholder recommendations to improve the current approach to HTA for drugs and their associated companion diagnostics dominated the recommendations advanced. As well, stakeholders made several recommendations related to society values that might inform policy development. While various recommendations were made, few described specific policy changes tied to a rationale explaining what problem would be addressed and how. It appears there may be more work needed to better define the problems and to fully develop and assess potential policy solutions.

- **Create a national HTA process for drugs and their companion diagnostics.** Many stakeholders identified the development of a national common review process for companion diagnostic tests similar to pCODR for oncology drugs or CADTH’s Common Drug Review for other drugs.⁵⁵ While stakeholders provided few specifics on how to develop such a national process, CADTH is now moving forward with the planned implementation of its HTA for drugs with companion diagnostics (see above for further details).
- **Increase the transparency of process and criteria.** Stakeholder recommendations for improving transparency included: publication of evaluation committee terms of reference, committee members and assessment reports;⁵⁶ clear guidance regarding the characteristics of tests that will be evaluated,⁵⁷ study design preferences, prioritization criteria; early guidance for innovators on evidence development; and an overview of the timing of reviews.⁵⁸
- **Improve stakeholder engagement in the HTA process.**⁵⁹ A 2012 report from the Institute for Health Economics suggested that changes to models of evaluation and uptake should involve “more upstream involvement of stakeholders”.⁶⁰ A 2016 academic publications recommended “better communication and collaboration between industry and HTA stakeholders” to improve diagnostics HTA.⁶¹ A 2016 publication in the *Provincial Reimbursement Advisor* recommended that “health technology agencies, public payers and hospitals should collaborate with drug and diagnostics developers to ensure funding evaluations and decisions also address the tests associated with therapies under review”.⁶² In light of the deficit of clear and standardized approaches, HTA policies that set the stage for health system adoption of drugs and their companion diagnostics should be informed by considered input from all key stakeholders.

⁵⁴ Slater, J., Shields, L., *et al.* (2015).

⁵⁵ Institute of Health Economics (IHE). (2012); CADTH. (2015); Gibson, S. & Lemmens, T. (2015); Garfield, S., Polisena, J., *et al.* (2016); Manion, R. & Dempster, B. (2016); Roche Consultancy Meeting on Personalized Medicine. (2016); Slater, J., Shields, L., *et al.* (2015).

⁵⁶ OPMN. (2014).

⁵⁷ OPMN. (2014); Garfield, S., Polisena, J., *et al.* (2016).

⁵⁸ Garfield, S., Polisena, J., *et al.* (2016).

⁵⁹ Institute of Health Economics (IHE). (2012); Manion, R. & Dempster, B. (2016); Garfield, S., Polisena, J., *et al.* (2016).

⁶⁰ Institute of Health Economics (IHE). (2012).

⁶¹ Garfield, S., Polisena, J., *et al.* (2016).

⁶² Manion, R. & Dempster, B. (2016).

- **Develop approaches to achieve “social return” on investment.** It was suggested that any HTA approach would “need to reflect society’s values while managing the inevitable conflict that will exist between these values versus science and evidence-based medicine” and that approaches to achieve a social return on national investments in personalized or precision medicine are needed.⁶³
- **Improve HTA methods to support equity and affordability.** A need to understand how HTA approaches can support affordability and equity of access was raised in the 2012 Institute of Health Economics Report.⁶⁴ Setting a target pharmaco-economic value as a cut-off for the adoption of new technologies was indicated in one document as a potential way of defining clearly what constitutes value for the healthcare system while better aligning public and private sector efforts to adopt new technologies.⁶⁵ HTAs should also explicitly recognize and provide a rationale for different approaches to evaluating a companion diagnostic based on whether it is a commercial diagnostic device regulated by Health Canada versus an LDT that is not subject to such regulatory oversight, as well as whether the outcomes of HTAs are consistently applied to each type of test.⁶⁶

4. Funding

Stakeholders noted that the absence of a standard HTA process for drugs and their companion diagnostics in Canada has impacted funding decisions made by ministries of health and healthcare institutions.⁶⁷ Payers rely on the recommendations provided by HTA evaluators in order to decide whether to fund a specific drug and / or its companion diagnostic. Many of the evidentiary challenges raised above respecting HTA – such as gaps in evidence about the clinical utility of the companion diagnostic – arise again in discussions about funding.

Following the HTA recommendation, payers who wish to add the drug to their formulary may begin negotiations through the pan-Canadian Pharmaceutical Alliance, which conducts joint negotiations for innovative medicines on behalf of interested jurisdictions in Canada. Successful negotiations result in a letter of intent (LOI) that sets out the reimbursement terms, including the price that public payers will pay for the drug. However, each jurisdiction must then separately enter into a product listing agreement with the manufacturer, built on the terms of the LOI, and add it to their formulary.

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.

Challenges

Key challenges identified by stakeholders related to funding of companion diagnostics include the absence of a link between drug and diagnostic funding within health budgets, industry subsidies for companion diagnostics, and challenges presented by the management of health technologies and the

⁶³ Slater, J., Shields, L., *et al.* (2015).

⁶⁴ Institute of Health Economics (IHE). (2012).

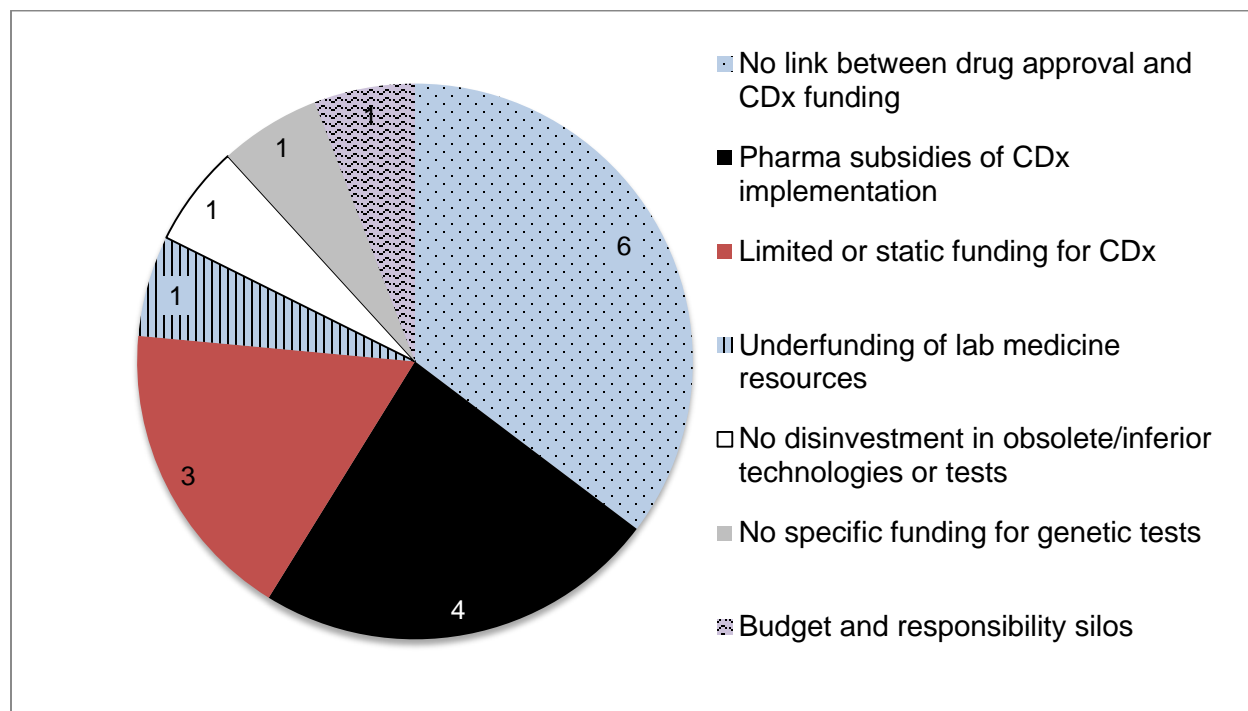
⁶⁵ McCabe, C., & Husereau, D. (2014).

⁶⁶ Garfield, S., Polisena, J., *et al.* (2016).

⁶⁷ Manion, R. & Dempster, B. (2016).

allocation of resources within existing budgets (see Table 5 below). This has been noted as hampering the adoption of innovation.⁶⁸

Table 5. Challenges Posed by the Current Approach to Funding



- **There is no link between regulatory authorization and funding of a drug and implementation of its companion diagnostic.** The most commonly cited problem concerning the funding of companion diagnostics was the lack of any sort of link between the regulatory authorization and funding of a drug and funding for implementation and delivery of an associated companion diagnostic.⁶⁹ This issue was described both as a disconnect between the drug budget and the laboratory services budget – either in the ministry of health budget or that of a healthcare institution (e.g., hospital): “[c]ompanion diagnostic funding and decision-making authority typically reside with institutional laboratory services budgets and controllers, while oncology drugs are primarily funded by provincial pharmaceutical budgets.”⁷⁰ Stakeholders also described this issue as a disconnect between regulatory authorization of a drug and operational funding for the test: “[t]here is no stated process or pathway to obtain reimbursement for its companion diagnostic as part of the reimbursement process of the drug.”⁷¹ One stakeholder clearly articulated the consequences of this disconnect for patients:

“This disconnect between funding of a drug and its predictive biomarker test resulted in a situation where there was no mechanism for mutation testing when gefitinib was approved for use in EGFR

⁶⁸ MEDAC Laboratory Medicine Stakeholders. (2015).

⁶⁹ Dawe, D. E. & Ellis, P. M. (2012); CADTH. (2014; partially updated 2016); CADTH. (2015); Manion, R. & Dempster, B. (2016); Roche Consultancy Meeting on Personalized Medicine. (2016); Slater, J., Shields, L., *et al.* (2015).

⁷⁰ Slater, J., Shields, L., *et al.* (2015).

⁷¹ Manion, R. & Dempster, B. (2016).

mutated patients. This disconnect in funding meant that there were very few labs capable of performing the molecular test, which therefore limited access to both the test and the drug.”⁷²

- **The pharmaceutical industry has subsidized companion diagnostic implementation.** The disconnect between drug and diagnostic budgets has, in some cases, led to the pharmaceutical manufacturer subsidizing the implementation and provision of the companion test. Several stakeholders noted that this practice has been problematic.⁷³ For example, when AstraZeneca supported pan-Canadian EGFR testing for the implementation of gefitinib, there was rapid uptake during the 12 months that testing was subsidized and a rapid and major decline at the end of the subsidy program.⁷⁴ The existence of such subsidies is not viewed as a sustainable solution.⁷⁵ It is also seen as undesirable because manufacturers determine their own funding criteria, which may not be aligned with providers’ views of best practice (e.g., only funding testing for patients that qualify for the particular therapy).⁷⁶ Although manufacturers have an interest in ensuring that testing is available for patients who may benefit from their drug, reliance on industry to fund diagnostic testing compromises the role and autonomy of healthcare systems in providing optimal care for patients.
- **Limited or static funding is currently available for companion diagnostic tests.** Inadequate funding for companion diagnostics suggests a possible under-valuing of these tests by healthcare systems. For healthcare institutions, such as hospitals, which receive block funding from provincial governments, “[a]ny tests and services offered, including genetic tests, must therefore be subsumed within the available budget, because provincial governments do not provide specific reimbursement for them” or the resources that support the use of a companion diagnostic, such as proficiency evaluation, training and development of new testing protocols.⁷⁷
- **Laboratory medicine resources are underfunded.** In the absence of adequate funding for laboratories to provide testing services, laboratory medicine stakeholders have noted understaffing, increased reliance on aging equipment, and overextending the lifespan of instruments, “resulting in higher costs to manage aging equipment than replace equipment (e.g., life cycle management vs. crisis management).”⁷⁸
- **There is no regular disinvestment in obsolete or inferior technologies.** Current practices do not include regular disinvestment of obsolete or inferior technologies or treatments for which updated or more advanced technologies or treatments exist.⁷⁹ Given finite resources, additional funding could be made available through this life-cycle management approach to health technologies.
- **There is no specific funding for genetic tests.** One stakeholder noted that the lack of specific funding for genetic tests is problematic.⁸⁰

⁷² Dawe, D. E. & Ellis, P. M. (2012).

⁷³ Dawe, D. E., & Ellis, P. M. (2012); CADTH. (2014; partially updated 2016); OPMN. (2014); Butts, C., Kamel-Reid, S., *et al.* (2013).

⁷⁴ Dawe, D. E., & Ellis, P. M. (2012).

⁷⁵ Butts, C., Kamel-Reid, S., *et al.* (2013).

⁷⁶ CADTH. (2014; partially updated 2016).

⁷⁷ Butts, C., Kamel-Reid, S., *et al.* (2013); CADTH. (2014; partially updated 2016); MEDAC Laboratory Medicine Stakeholders. (2015).

⁷⁸ MEDAC Laboratory Medicine Stakeholders. (2015).

⁷⁹ Slater, J., Shields, L., *et al.* (2015).

⁸⁰ Butts, C., Kamel-Reid, S., *et al.* (2013).

- **Budget and responsibility silos.** This problem refers to a variety of situations where decision-making about the evaluation and funding of a drug and its companion diagnostic are not coordinated, which leads to problems for healthcare system implementation of the drug-companion diagnostic pair.⁸¹ A lack of connection between the responsibilities for evaluating and authorizing a test for use and allocating funding can mean that tests with demonstrated clinical value that are authorized for use in Canada, a province or at a particular institution, cannot be fully or well implemented due to a lack of funding to do so. The absence of or a weak connection between the evaluation and funding of a drug and an associated companion diagnostic can contribute to three different situations: (1) the drug is available in a particular health care system but funding is not allocated for the companion diagnostic; (2) it is not clear which companion diagnostic (e.g., device or LDT) should be recommended for use; or (3) it is not clear which of any available companion diagnostics are adequate for safe and effective use with the approved drug.

Recommendations

As with the HTA category (above), recommendations for addressing the challenges posed by the current approach to funding were not specific or detailed. It was suggested that creating a link between HTA and companion diagnostic funding could help but how this could be achieved was not clearly described,⁸² including through the elimination of budget silos,⁸³ nor were policy or operational strategies for creating such a link fully articulated.

However, two concrete recommendations were advanced by stakeholders to improve standardization and consistency of funding of companion diagnostics.

- **Establish a national oversight body to review, interpret and provide recommendations about genetic tests.** One group of stakeholders proposed a National Genetics Advisory Panel to provide recommendations that would support the establishment of “appropriate financial parameters for funding by delineating requirements for appropriate application of tests” including funding and delisting recommendations and “developing an appropriate cost model for each test as a benchmark.”⁸⁴
- **Fund multi-centre standardization of each companion diagnostic.** Each new test requires funding to be standardized across multiple centres prior to being incorporated into existing platforms.⁸⁵

5. Health System Delivery

Once a funding decision has been made to make a companion diagnostic available with its associated drug, stakeholders have noted various challenges to the actual delivery of the test in the health system. Outside the actual operation of laboratories, these issues reflect the multiple health system stakeholders involved in identifying patients who are eligible for the tests and referring them for the test.

⁸¹ MEDAC Laboratory Medicine Stakeholders. (2015).

⁸² Dawe, D. E. & Ellis, P. M. (2012); Garfield, S., Polisen, J., *et al.* (2016).

⁸³ MEDAC Laboratory Medicine Stakeholders. (2015).

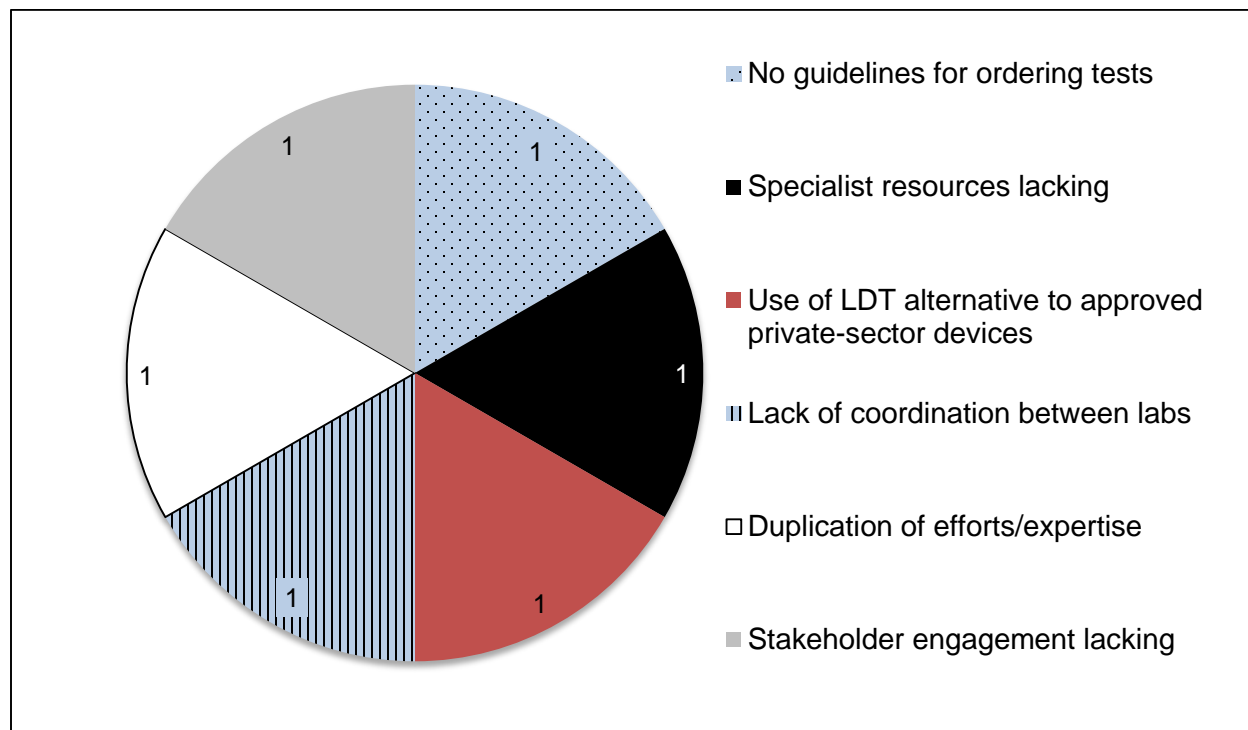
⁸⁴ Butts, C., Kamel-Reid, S., *et al.* (2013).

⁸⁵ Canadian Cancer Research Alliance & Robbins, S. (2015).

Challenges

In contrast with the topics above, there was no duplicate mention of distinct challenges posed by the current approach to delivering companion diagnostics (see Table 6 below).

Table 6. Challenges Posed by Current Approach to Health System Delivery



- **Stakeholders report that there are no guidelines for ordering tests.**⁸⁶ Healthcare providers would benefit from guidance on how to provide patients with access to companion diagnostics.
- **Specialist resources are lacking.** One stakeholder commented on this issue in relation to lung cancer: “The need for improved diagnostic lung cancer samples has major resource implications in a national healthcare system affecting thoracic surgeons, respirologists, interventional radiologists and pathologists.” As well, the stakeholder noted that “[l]imited numbers of specialists and finite operating room time make it difficult to scale up the number of procedures to collect adequate tissue.”⁸⁷
- **Laboratories may use diagnostic tests developed in-house rather than proprietary tests.** The lack of clarity around which tests are used – and whether they are regulated by Health Canada or subject to any other analyses, such as HTAs – was noted by one stakeholder as creating “a more confusing landscape for industry, health system decision-makers, health care providers and patients to navigate in the absence of a clear access pathway.”⁸⁸

⁸⁶ MEDAC Laboratory Medicine Stakeholders. (2015).

⁸⁷ Dawe, D. E. & Ellis, P. M. (2012).

⁸⁸ Manion, R. & Dempster, B. (2016).

- **There is a lack of coordination among laboratories that provide companion diagnostic testing.** The Ontario Personalized Medicine Network noted that the “current distribution of tests amongst different sites lacks coordination, complicating quality control and access”.⁸⁹
- **There is duplication of efforts and expertise.** Arising out of the lack of coordination among laboratories, efforts are being duplicated and there is no specific way to link existing knowledge and expertise to support fellow laboratories.⁹⁰
- **Stakeholder engagement is lacking.** Laboratory initiatives require the support of other health system stakeholders, including physicians. Where engagement from them is lacking, the success of such initiatives can be “compromised”.⁹¹

Recommendations

Three themes emerged in the recommendations offered by stakeholders.

- **Centralize specialized laboratory services.** One stakeholder emphasized that “[t]he centralization of highly technical tests may be necessary to ensure the highest quality testing” although the processes used in such centralized locations must ensure access to those located further away.⁹² Another recommended the creation of a national network of public-sector ‘molecular diagnostics hubs’ with the specific objective of “reduc[ing] duplication of effort and facilitate[ing] quality assurance measures, as well as providing assistance to laboratories in need of additional support.”⁹³ Regulatory reforms may also be necessary to support such centralization.⁹⁴
- **Develop practice guidelines for laboratory services.** In order to realize the fruits of companion diagnostic technologies, “guidelines and service delivery models should also be developed that provide consistent standards for provinces and territories to follow ... [that include] recommendations on how to implement laboratory service logistics such as minimum volumes and guidelines that ensure quality and cost effectiveness.”⁹⁵ Such guidelines should include representation from laboratory medicine.⁹⁶
- **Coordinate the implementation of companion diagnostics.** The coordination and alignment of services providing personalized genomics testing was noted as essential to the delivery of such technologies.⁹⁷

⁸⁹ OPMN. (2014).

⁹⁰ Canadian Cancer Research Alliance & Robbins, S. (2015).

⁹¹ CADTH. (2014). Optimization of Laboratory Service, Draft Environmental Scan (Environmental Scan). Ottawa: CADTH. Retrieved from http://www.cadth.ca/media/pdf/ES2087_Lab_Optimization_Efforts-draft.pdf

⁹² Slater, J., Shields, L., *et al.* (2015).

⁹³ Canadian Cancer Research Alliance & Robbins, S. (2015).

⁹⁴ Institute of Health Economics (IHE). (2012).

⁹⁵ Butts, C., Kamel-Reid, S., *et al.* (2013).

⁹⁶ MEDAC Laboratory Medicine Stakeholders. (2015).

⁹⁷ Bashir, N. S., Ungar, W. J., & Jimenez-Sanchez, G. (2015). The 3-I framework: a framework for developing public policies regarding pharmacogenomics (PGx) testing in Canada 1. *Genome*, 58(12), 527–540. <https://doi.org/10.1139/gen-2015-0100>

6. Laboratory Oversight and Operations

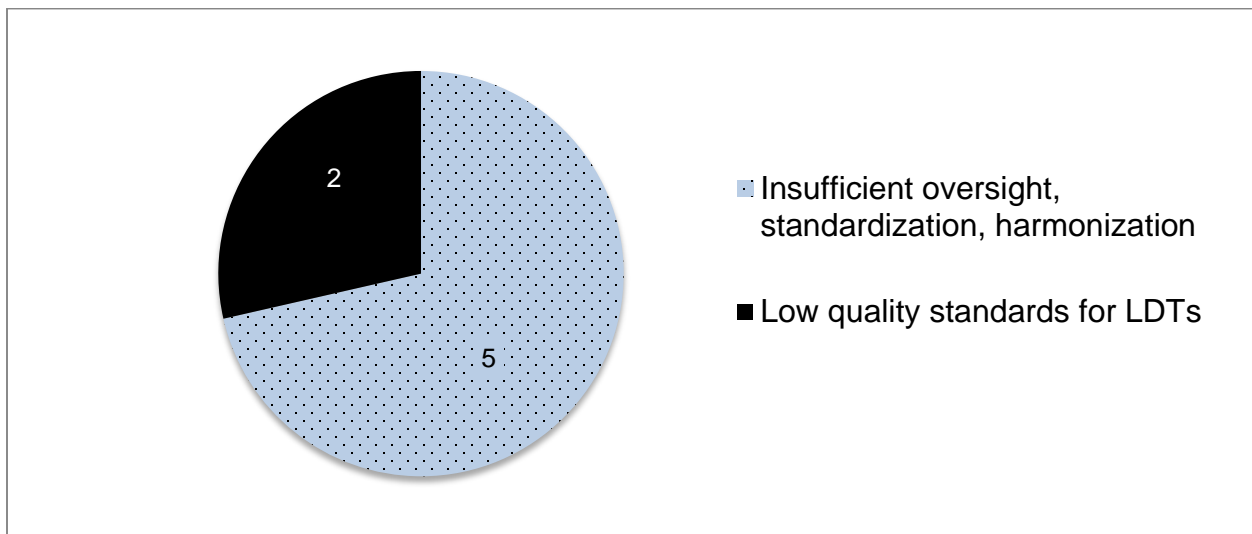
Stakeholders noted various issues that arise within the laboratory where the test is being conducted far less often than issues related to HTA, funding and health system delivery. However, challenges posed by current laboratory oversight and operations should be addressed as part of a comprehensive approach to improving patient access to companion diagnostics.

As noted above, laboratory services are not subject to federal regulation but are overseen by provincial authorities. While there are national standards, they are in the form of accreditation and are not mandatory so adherence to them varies across the country.

Challenges

Almost all of the stakeholders who analyzed the impact of laboratory operations on access to companion diagnostics described a cluster of related problems, including a lack of laboratory oversight, standardization of operations/testing and of harmonization of oversight/standardization nationally (see Table 7 below).

Table 7. Challenges Posed by Current Approach to Laboratory Oversight and Operations.



- **There is insufficient oversight, standardization, and harmonization across Canada.** Stakeholders confirmed that there are no national standards that guide laboratory services.⁹⁸ A CADTH-led roundtable noted “agreement that some national requirements for clinical laboratory accreditation applicable to LDTs should exist.”⁹⁹
- **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

⁹⁸ Butts, C., Kamel-Reid, S., *et al.* (2013); Roche Consultancy Meeting on Personalized Medicine. (2016); Manion, R. & Dempster, B. (2016); Canadian Cancer Research Alliance & Robbins, S. (2015).

⁹⁹ CADTH. (2015).

quality standards that apply to LDTs and those that apply to diagnostics regulated by Health Canada (e.g., as test kits).¹⁰⁰

Recommendations

Stakeholder recommendations to address the variability in laboratory operations and gaps in oversight called for greater regulation of the sector, particularly as it relates to quality assurance of companion diagnostics.

- **Increase regulation of quality assurance.** Several stakeholders recommended an increase in regulation of quality assurance of molecular testing. A 2013 article suggested “establishing standards and processes for proficiency testing for specific genetic tests and a laboratory quality management program in the form of a national external quality assurance program”.¹⁰¹ A 2015 article suggested that there is “clearly a need for some level of regulatory scrutiny in considering where and how tests are conducted”.¹⁰² The same article further recommended oversight of testing sites, methods used by testing sites and adherence to laboratory guidelines and best practices. As noted above, there was agreement at a meeting hosted by CADTH that “national requirements for clinical laboratory accreditation applicable to LDTs should exist” and a need for “development of national accreditation requirements for clinical laboratories”.¹⁰³ This meeting report describes a number of areas of consensus including development and implementation of a pan-Canadian proficiency testing program.

¹⁰⁰ Gibson, S., & Lemmens, T. (2015); OPMN. (2014).

¹⁰¹ Butts, C., Kamel-Reid, S., *et al.* (2013).

¹⁰² Gibson, S., & Lemmens, T. (2015).

¹⁰³ CADTH. (2015).

CONCLUSION

This review highlights a variety of challenges and opportunities. Individual issues and processes should be considered as part of a dynamic system. There are many overlapping and inter-related relationships between regulators, industry, health technology assessors, health system decision-makers, payers, healthcare providers and patients. While this report began to articulate these relationships, they are constantly evolving in response to scientific advances and related policy responses. Efforts must be made to continue to describe and understand these relationships and their implications for patient access to promising therapies and their companion diagnostics in Canada.

In general, many recommendations proposed by stakeholders are high-level and further exploration and analysis is necessary in order to understand how specific recommendations would be implemented and their resulting risks and opportunities. Input from all stakeholders will ensure coherent policies and processes. In particular, important value-based drivers are not presently well defined. Understanding the values underlying different policy approaches will be important as well.

To a certain extent, CADTH appears to be assuming a pan-Canadian role in providing recommendations about companion diagnostics in the context of reviews of their associated drugs through its new HTA process. CADTH also has other services that can be leveraged by health system leaders to provide clinical and economic guidance for funders of companion diagnostics. These initiatives should provide support for companion diagnostics policy of provincial governments and healthcare institutions.

In order to advance this issue, we encourage health system policy makers to view these challenges and recommendations as a practical exercise with tangible implications for stakeholders and – in particular – for Canadian patients. To this end, included in this draft is a discussion guide with key questions to validate the findings, including guiding principles for a stakeholder alliance to encourage discussion with a view to addressing the challenges of the current approach to companion diagnostics in Canada.

DISCUSSION GUIDE

Questions for Discussion

- Do Canadian stakeholders have a comprehensive and accurate understanding of challenges/problems related to health care system implementation of CDx (i.e. regulatory approval, evaluation, funding and laboratory operations)?
- What are the high-priority challenges, why, what are the areas of consensus or contention amongst stakeholder types?
- What are potential approaches or solutions to address the identified and prioritized challenges, what are the areas of consensus or contention amongst stakeholder types?
- The value of the CDx tests appears dwarfed in reimbursement scenarios, by the much higher cost of the drug. What are the implications of this? What might a stakeholder alliance do to work toward policy-solutions to this problem?
- Is assigning a value to the test the only way to address current issues with static funding for tests? How do we change the conversation from a sole consideration of impact on budget vs cost-effectiveness? How do we assign clinical or economic value to a CDx or how to distinguish this value from a similar value for a drug? What might a stakeholder alliance do to work toward policy-solutions to this problem?
- How should/can meaningful input from patients (the most important stakeholder) be integrated as we move forward in addressing policy issues related to CDx?

Guiding Principles for CDx Stakeholder Alliance

Goal: to align different stakeholders around the same objectives

1. Access to companion diagnostics is crucial to patient access to medicines.
2. The adoption of companion diagnostics in the health system must be based on evidence and designed to respond to the rapid pace of scientific advances.
3. All stakeholders benefit from clarity around how the health system adopts companion diagnostics.

APPENDICES

Appendix 1. Approved Companion Diagnostics in Canada

Source: CADTH. (2014; partially updated 2016). *Environmental Scan, Pharmaceuticals Requiring Companion Diagnostics, Appendix 1 and Appendix 2.*

Device Trade Name and Companion Drug	Tumour Type / Indication	Approval Status		
		Health Canada MDALL	FDA (USA)	CE-IVD Marked (Europe)
Therascreen KRAS RGQ PCR Kit Erbix (cetuximab)	Gastrointestinal; metastatic colorectal cancer	Approved First Issue Date: 2009-05-08	Approved	Approved
Dako EGFR pharmDx Kit Erbix (cetuximab); Vectibix (panitumumab)	Colorectal cancer	Approved First Issue Date: 2004-11-23	Approved	Approved
Therascreen EGFR RGQ PCR Kit Giotrif / Gilotrif (afatinib)	Advanced non-small cell lung cancer	N/A	Approved	Approved
Dako c-Kit pharmDx Gleevec / Glivec (imatinib mesylate)	GIST	Approved First Issue Date: 2006-02-08	Approved	Approved
Inform HER2/neu Herceptin (trastuzumab)	Breast cancer	N/A	Approved	Approved
PathVysion HER-2 DNA Probe Kit Herceptin (trastuzumab)	Breast cancer	Approved First Issue Date: 1999-03-26	Approved	Approved
PATHWAY anti-HER-2/neu (4B5) Rabbit Monoclonal Antibody Herceptin (trastuzumab)	Breast cancer	Approved First Issue Date: 2006-12-27	Approved	N/A
SPoT-Light HER2 CISH Kit Herceptin (trastuzumab)	Breast cancer	Approved First Issue Date: 2006-03-17	Approved	Approved
BOND Oracle HER2 IHC System Herceptin (trastuzumab)	Breast cancer	N/A	Approved	N/A
HER2 CISH pharmDx Kit Herceptin (trastuzumab)	Breast cancer	Approved First Issue Date: 2010-09-29	Approved	Approved
Inform HER2 Dual ISH DNA Probe Cocktail Herceptin (trastuzumab)	Breast cancer	Approved First Issue Date: 2011-11-04	Approved	Approved
HercepTest Herceptin (trastuzumab);	Breast cancer; Metastatic breast cancer	Approved First Issue Date: 2013-09-26	Approved	Approved

Device Trade Name and Companion Drug	Tumour Type / Indication	Approval Status		
		Health Canada MDALL	FDA (USA)	CE-IVD Marked (Europe)
Perjeta (pertuzumab); Kadcyla (ado-trastuzumab emtansine)				
HER2 IQFISH pharmDx Kit Herceptin (trastuzumab); Perjeta (pertuzumab); Kadcyla (ado-trastuzumab emtansine)	Breast cancer; Metastatic breast cancer	Approved First Issue Date: 2004-08-30	Approved	Approved
THxID-BRAF Kit Mekinist (trametinib); Tafinlar (dabrafenib)	Melanoma; Metastatic melanoma	Approved First Issue Date: 2013-11-19	Approved	Approved
cobas EGFR Mutation Test Tarceva (erlotinib)	Metastatic non-small cell lung cancer	Approved First Issue Date: 2014-03-18	Approved	Approved
Vysis ALK Break Apart FISH Probe Kit Xalkori (crizotinib)	Advanced non-small cell lung cancer	Approved First Issue Date: 2012-03-14	Approved	Approved
cobas 4800 BRAF V600 Mutation Test Zelboraf (vemurafenib)	Melanoma; advanced melanoma	Approved First Issue Date: 2011-11-10	Approved	Approved
Oncotype DX Breast Cancer Assay – Laboratory Diagnostic Test	Breast cancer	N/A Note: The test is currently reimbursed publicly in Ontario, Quebec, and Saskatchewan, with a number of provinces considering public funding for qualified breast cancer patients. ¹⁰⁴	Approved – CLIA— 05D10182 72	N/A

¹⁰⁴ New research shows genomic testing changes chemotherapy treatment decisions in British Columbia breast cancer patients by 30 per cent [Internet]. Toronto: Genomic Health, Inc.; 2012 Jul 9. [cited 2015 Sep 15]. Available from: <http://news.cision.com/genomic-health--inc-/r/new-research-shows-genomic-testing-changes-chemotherapy-treatment-decisions-in-british-columbia-brea,c9282478>

Appendix 2. Methodology Notes

Sixteen articles or reports published in the last 5 years (2012-2016) that express Canadian stakeholder opinions on policy or operational problems related to Canadian healthcare system evaluation, funding and delivery of companion diagnostic tests were identified. Text expressing problems related to the area of interest or recommendations for addressing such problems was extracted and collated using Excel. This text was then categorized based on the following topics: health system adoption pathway, regulatory authorization, health technology assessment (HTA), funding, healthcare system delivery, or laboratory oversight and operations when the problem related to two or more of the listed topics. Redundant expressions of equivalent meaning were merged and counted only once per document.

The affiliations of authors or contributors in the case of meeting reports were also extracted. Seventy-two different Canadian stakeholder organizations are represented in the set of documents. Those represented more than twice are listed in Table 8 (see below). An analysis of the type of stakeholder involved in the creation of each document was also conducted (see Table 9 below).

Table 8. Stakeholder Representation

Stakeholder Organization	Times Represented
Canadian Agency for Drugs and Technologies in Health (CADTH)	7
Diagnostic Services Manitoba	5
University of Toronto	5
Canadian Institutes of Health Research (CIHR)	4
Alberta Health Services	4
Roche Diagnostics	3
Ontario Ministry of Health and Long-Term Care	3
BC Cancer Agency	3
Canadian Partnership Against Cancer	3

Table 9. Stakeholder Type

Sector	Stakeholder Type	Times Represented
Public	Provider	35
Public	Academic	25
Private	Diagnostics Company	12
Public	HTA Body	11
Public	Research Funding	9
Public / NPO	Advocacy	6
Public	Centre of Excellence-Network	5
Public	Policy Maker	5
Private	Pharmaceutical Company	3
Private	Consulting Firm	1
	TOTAL	112