

CADTH Horizon Scan

# An Overview of Comprehensive Genomic Profiling Technologies to Inform Cancer Care

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## Key Messages

- Horizon Scan reports provide brief summaries of information regarding new and emerging health technologies; Health Technology Update articles typically focus on a single device or intervention. This Horizon Scan summarizes the available information regarding emerging comprehensive genomic profiling (CGP) technologies for informing cancer treatments.
- These technologies are based on next-generation sequencing platforms, which can characterize up to hundreds of genes and other genomic information with a single sample. Emerging tests are also compatible with minimally invasive liquid biopsies that use fluids such as blood samples to support clinical decision-making. CGP could be an alternative or a complement to conventional testing that uses single-biomarker assays or limited gene panels.
- Some emerging CGP tests available in Canada, the US, and Europe are being considered to inform the treatment of non–small cell lung cancer (NSCLC) because it has the highest number of identified biomarkers. Most identified studies have examined CGP use with NSCLC.
- The emerging evidence about the clinical and cost-effectiveness of CGP technologies for either NSCLC or other cancer types remains uncertain. Without randomized trials and robust study designs, it is not yet well-established whether the additional costs and technical requirements of CGP may provide better clinical outcomes compared with conventional molecular testing.
- This Horizon Scan also provides considerations for health systems about testing infrastructure, training for health care professionals, and understanding different patients' perspectives should CGP or other next-generation sequencing technologies become more widely used in Canada.

## Purpose

The purpose of this Horizon Scan is to present health care stakeholders in Canada with an overview of information related to liquid biopsy–based comprehensive genomic profiling (CGP) technologies for informing cancer treatments, a description of some of the published studies, and a summary of some important considerations. These findings are intended to inform stakeholders should emerging evidence and clinical guidelines indicate the technology can demonstrate value and be used as part of routine care. This report is not a systematic review and does not involve critical appraisal or include a detailed summary of study findings. It is not intended to provide recommendations for or against the use of the technology.

## Methods

### Literature Search Strategy

A limited literature search was conducted by an information specialist on key resources, including MEDLINE, Embase, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The main search concepts were liquid biopsy and

comprehensive genomic profiling. No filters were applied to limit the retrieval by study type. Case studies were excluded. The search was also limited to English-language documents published between January 1, 2019, and March 25, 2022. Regular alerts updated the search until project completion; only citations retrieved before May 30, 2022, were incorporated into the analysis. Few relevant studies published before 2019 were included for additional context.

## Study Selection

One author screened the literature search results and reviewed the full text of all potentially relevant studies. Studies were considered for inclusion if the intervention was CGP used for cancer treatment selection. Additional studies related to the broader concept of next-generation sequencing (NGS), molecular profiling, liquid biopsy, and genetic testing were included if they were related to the primary concept. Studies of genomic tests used for cancer screening or tests without direct clinical implications (such as validation studies of cell samples) were not included. Conference abstracts and grey literature were included when they provided additional information to that available in the published studies.

## Peer Review

A draft version of this bulletin was reviewed by 1 clinical expert with expertise in medical oncology. Two manufacturers were given the opportunity to comment on an earlier draft and provided their input.

## Background

Health care services that consider an individual's unique molecular profile and other aspects about their lifestyle and environment are referred to as [precision medicine](#). Rather than a one-size-fits-all approach, certain aspects of disease prevention and treatment are tailored for people based on their individual characteristics. Although precision medicine has seen increasing growth across different health conditions in Canada, cancer care continues to have the greatest level of innovation due to the different molecular subtypes and actionable targets for certain cancers.<sup>1</sup> Emerging NGS technology to profile the genetic make-up of individuals with cancer represents the next possible wave of innovation. It may expand the scope of precision medicine and facilitate health care that incorporates greater data resolution to inform patient-centred care and treatment.<sup>2</sup>

Many treatments require companion diagnostics, which are medical devices that assess essential information about the safe and effective use of a corresponding drug or biological product.<sup>3</sup> Most companion diagnostics assess a single-gene or protein biomarker to support treatment.<sup>4,5</sup> These tests are highly accurate, can be performed in-house at many hospitals, and may provide timely results (within hours or days). However, single-gene assays cannot test multiple genes simultaneously or assess a broad range of genomic changes.<sup>6,7</sup> An alternative to single-biomarker tests is CGP, a specific type of NGS technology. While NGS covers a range of different platforms, CGP refers to tests that examine a large panel of genes — in some cases hundreds of genes — and may detect global genomic changes to inform cancer treatment decisions and provide information about prognosis and disease monitoring.<sup>2</sup> Many of these emerging tests are being developed to analyze cell-free DNA (cfDNA) and circulating tumour DNA (ctDNA) from liquid biopsy samples rather than cancer

tissue biopsy samples. This expands access to people for whom tissue biopsy may not be feasible due to safety concerns or challenges in accessing the tumour.<sup>6,7</sup> The use of liquid biopsy may also provide additional information about the cancer, such as tumour heterogeneity, that may not be detectable with tissue-based assays.<sup>6,7</sup> CGP may help expand the use of precision medicine into routine care, and could provide more data and information to help guide treatment decisions for people with cancer.<sup>2,8,9</sup> However, the technology is still relatively new and is not part of the current standard of care. The evidence about the clinical and cost-effectiveness of these tests is beginning to emerge. This Horizon Scan provides an overview of the technology, a summary of some studies, and perspectives on early considerations should emerging evidence demonstrate the value of CGP.

## The Technology

Certain gene mutations (alterations in DNA) can increase the risk of developing different cancers in susceptible people or affect how a cancer manifests, progresses, and develops resistance to therapies.<sup>10</sup> Mutations may occur across the genome affecting protein-coding genes and gene expression and in non-coding DNA.<sup>10</sup> Although the full extent of mutations, whether inherited (germline) or occurring after conception (somatic), can be complex and varied; only a subset will have clinical significance associated with specific cancers. Different cancers may be associated with germline or somatic mutations. For example, germline mutations in the *BRCA1* and *BRCA2* genes are associated with a predisposition to breast cancer and aggressive subtypes of the disease. Therefore, some people with breast cancer can benefit from therapy targeting *BRCA1/BRCA2* mutations.<sup>11,12</sup> Somatic mutations accumulate over time and can be associated with the development and progression of cancers.<sup>13</sup> Importantly, many somatic mutations can be associated with biological changes that have implications for treatment selection.<sup>10</sup> For example, several therapies target mutations in the *EGFR* gene in people with non-small cell lung cancer (NSCLC) are associated with beneficial clinical outcomes.<sup>14</sup>

However, sequencing the entire genome or the exome (the protein-coding regions) is costly and provides more data than required for providing clinically meaningful information in routine care.<sup>15</sup> Therefore, the goal of companion diagnostic devices is to characterize specific genomic changes that are actionable; meaning, they can directly inform treatment selection.<sup>10</sup> Some mutations can also be driver mutations, which means they may not be directly targetable with a therapy but can be associated with drug resistance or cancer progression and provide useful information about treatments.<sup>10</sup> Approximately, 200 biomarkers have been identified across cancer types that can inform specific treatment pathways.<sup>2</sup> A review of 44 companion diagnostic devices approved by the FDA in the US reported that polymerase chain reaction (PCR) technology that detects primarily single genes (some PCR assays are also able to detect a limited gene panel) made up the largest share of companion diagnostics followed by fluorescent DNA probes.<sup>4</sup> Tests that detect immunological markers are also common, but these are not designed to detect genomic changes. Companion diagnostic tests using NGS technology emerging since 2017 may help reduce the need for individual tests to assess each biomarker.<sup>4,6</sup>

## Emerging Tests Detect a Variety of Genomic Changes

NGS technology allows for increasing the output of sequencing to characterize more areas of the genome.<sup>16</sup> Tests that use NGS are capable of identifying a variety of genomic changes including single point mutations, insertions, and deletions in multiple genes with a single sample.<sup>2</sup> They can also characterize global genetic alterations that cannot be detected by single-gene or PCR-based assays. These global genomic changes may include copy number variation, mutations in microsatellites, and the total amount of somatic mutations (tumour mutation burden), all of which may have implications for cancer diagnosis, therapies, and prognosis.<sup>6,17</sup> CGP could have increasing importance within precision medicine as a growing list of biomarkers are being identified to inform treatment selection. Rather than a single mutation informing a single drug, CGP could help identify multiple mutations, their potential interaction, and other factors that may help indicate the most suitable therapeutic option for people. For example, more than a dozen therapies targeting different mutations across several genes have been developed for NSCLC.<sup>18,19</sup> A single test that detects multiple mutations could also be used for a variety of different cancers and streamline some aspects of clinical investigation.

Commercial CGP devices that assess a panel of genes and provide specific testing kits are classified as “in vitro diagnostic devices” and are required to have regulatory approval in Canada, the US, and Europe.<sup>20,21</sup> Tests developed in-house at hospitals or other clinical settings are considered laboratory tests that may not require regulatory approval.<sup>20,22</sup> CGP tests could potentially be used as a companion diagnostic for different therapies and may be available for either tissue or liquid biopsy samples, depending on the technical requirements.<sup>16,23</sup> The primary focus of this Horizon Scan is liquid biopsy-based CGP tests. Some identified examples of emerging CGP devices include:

- [FoundationOne Liquid CDx](#) (Foundation Medicine Inc., US) profiles 324 genes, tumour mutation burden, and other genomic information. The test is authorized by the FDA as a companion diagnostic for drugs that may inform treatment for people with NSCLC, prostate, ovarian, and breast cancers.<sup>24</sup>
- [Guardant360 CDx](#) (Guardant Health, US) profiles 55 genes and is authorized by the FDA as a companion diagnostic that may inform treatment for people with NSCLC and other advanced solid tumours.<sup>24</sup>
- [Follow It](#) (Imagia Canexia Health, Canada) profiles 38 genes and is potentially able to characterize biomarkers that can inform treatments for breast, colorectal, NSCLC, and other cancers.

## Strengths and Limitations of Tissue Versus Liquid Biopsy

Testing kits and platforms for CGP tests have unique technical requirements based on whether tissue or liquid biopsy samples are used. Each sample type has its own strengths, limitations, and implications that can affect its potential use. Tissue biopsy is the most widely used approach for biomarker testing and remains the gold standard for genomic testing of solid tumours.<sup>25</sup> Tissue samples allow for analyzing both genomic changes and histological and immunological markers (such as cell surface markers like PD-L1) directly from the tumour.<sup>26</sup> Since genetic material (DNA or RNA) is extracted from the cancerous tissue, traditional amplification techniques (such as PCR) can reliably characterize specific genes quickly and at a lower cost than NGS technology when examining individual genes.<sup>2,16</sup> However, tissue biopsies are also inherently limited because tissue sampling may not be feasible among people with advanced cancers for whom biopsies could have additional

safety risks.<sup>25</sup> Additionally, tissue-based samples are collected at 1 time point and can be challenging to collect repeatedly if required to monitor changes in the cancer or to examine multiple biomarkers. Tissue exhaustion may limit the number of repeat samples that can be collected for further tissue-based assays.<sup>27</sup> Some tissue-based CGP tests are emerging that can detect multiple genes at once, which may help reduce some of these limitations. For example, the [OncoPrint Comprehensive Assay](#) (Thermo Fisher Scientific, US) can profile more than 500 genes, and both Foundation Medicine and Imagia Canexia Health have tissue-based CGP assays that characterize a similar panel of mutations as their liquid-based tests, but with different sampling requirements.

In contrast, CGP analysis based on liquid biopsies examines cfDNA found in blood or other bodily fluids (e.g., cerebrospinal fluid, urine, or pleural effusion from lungs) and aims to detect ctDNA.<sup>7</sup> ctDNA is released by cancerous tissues into the blood stream and is emerging as complementary to tissue-based samples.<sup>28</sup> Liquid biopsies may also be able to detect circulating tumour cells and other cellular components that could serve as biomarkers to inform treatment options.<sup>25</sup> Obtaining certain fluid samples, such as blood, can be less invasive and be associated with fewer complications, particularly if repeat samples are required.<sup>7</sup> Among people with advanced cancers or those with susceptible clinical conditions, a liquid biopsy can provide a safer and minimally invasive alternative to tissue biopsy.<sup>25</sup> Turnaround times between sample collection to results are also likely to be shorter with liquid biopsies.<sup>7,28,29</sup> Analysis of ctDNA can have additional functional uses, such as monitoring cancer progression, therapeutic response (e.g., resistance development), and possibly detecting early indications of recurrence through subsequent testing or longitudinal analysis.<sup>7,30</sup> However, because liquid biopsies do not directly target the primary tumour, they generally have reduced sensitivity compared with tissues samples, and, in some circumstances (e.g., certain cancer types, early-stage tumours, or patient-related factors), there may be limited ctDNA shed by tumours, which makes detection challenging.<sup>28,31</sup> Specificity of liquid biopsy-based tests has been reported to be high ( $\geq 90\%$ ) in most studies but it may still be prone to variability in different mutations and genes.<sup>31</sup> Sample preparation and handling of ctDNA may also affect analyses and can be prone to variability.<sup>30</sup> Many researchers have stated that the future role of liquid biopsy as standard of care for many cancer types remains uncertain and requires further validation and assessment.<sup>7,28,32,33</sup>

## Availability and Guidelines

CGP tests using liquid biopsies are available in Canada as part of research programs and they may be available as laboratory-developed tests.<sup>34</sup> A 2020 review of precision medicine within cancer care reported that most companion diagnostics in Canada are laboratory-developed tests which do not require regulatory authorization.<sup>22</sup> Although no information about the specific prevalence of CGP testing or availability across Canadian centres was identified, 1 review reported that research relating to the economics of NGS use in Canada has been growing.<sup>35</sup> Previously, the Canadian College of Medical Geneticists provided practice guidelines for NGS testing (not specific to cancer) with details about the need for standardized quality assessment for sample preparation, bioinformatics, clinical interpretation, and other technical aspects.<sup>36</sup>

Clinical guidelines about the potential use of NGS-based testing have been developed for a limited number of cancer types. For example, jointly developed guidelines by Ontario Health

and the American Society of Clinical Oncology recommend that people diagnosed with NSCLC (stage IV) should receive testing for all actionable targets; however, it did not specify that CGP testing should be used.<sup>37</sup>

At the time of writing, the most recent National Comprehensive Cancer Network (NCCN) guidelines (version 3.2022) from the US recommend molecular testing for people with metastatic NSCLC to characterize all actionable biomarkers.<sup>38,39</sup> The NCCN panel states that, when feasible, broad panel-based assays be used to assess established and emerging biomarkers.<sup>39</sup> However, the panel indicated that these assays may include both single assays that detect multiple biomarkers (as in the case of CGP test) or a combination of assays.<sup>39</sup> It also states that while most broad panel-based assays are based on NGS technology, other sequencing technologies may be used (e.g., Sanger or RT-PCR-based assays).<sup>39</sup> In addition, the NCCN panel recommends that liquid biopsy should be used if there is insufficient tissue available for tissue-based testing.<sup>38,39</sup>

The most comprehensive set of recommendations about NGS-based testing for various cancers that we identified were developed by the European Society for Medical Oncology (ESMO).<sup>18</sup> Their recommendations provide guidance about whether NGS tests with multi-gene panels (such as CGP) could be used for different metastatic cancer types as part of routine care. The working group developed guidance based on evidence about actionable genomic changes among cancer types associated with the highest numbers of deaths. The guidelines state that NGS tests with multi-gene panels can be used for people with advanced NSCLC, prostate, ovarian, and bile duct cancers if the cost is within an acceptable local level.<sup>18</sup> Liquid biopsy-based NGS testing options were mentioned for NSCLC, but no recommendation was listed about use with other cancers. NGS may also be used as an alternative to PCR for colon cancers provided it does not incur additional costs of routine testing.<sup>18</sup> For other cancers, such as breast, colorectal, gastric, pancreatic, and liver cancers, NGS testing is not recommended due to the limited number of clinically meaningful targets and the relatively lower cost and ease of testing with PCR or other molecular techniques.<sup>18</sup> However, NGS testing may be used for different cancers as part of clinical research to identify potential candidates of newer targeted therapies.

## Cost

When calculating the budget impact of CGP testing on health systems, the cost of the tests and laboratory overhead must be considered in addition to how the tests are used as part of clinical pathways (e.g., as a triage test, complement to other tests, or limited to specific circumstances).<sup>9</sup> Sample collection and analysis, testing infrastructure, the need for sufficient volume of tests, determining which cancer types may be eligible for testing, and the effect on access to targeted therapies will be important for estimating overall cost implications for health systems.<sup>9,27,40</sup>

The costs of different tests may not be comparable because they may have different analysis capabilities and/or requirements for sending samples to central laboratories or performing in-house analysis or assessing different genomic features. As such, prices of some tests presented in this report are not for direct comparison but to provide a general indication about the variability in potential costs. Current costs may vary from what were reported in published studies.

A Canadian study using a CGP-based test (OncoPrint v3, a tissue-based test) reported a total cost of \$1,322 per sample for testing NSCLC.<sup>41</sup> Although the specific test had a cost of \$420, additional costs included sample preparation, data processing and analysis, and laboratory overhead.<sup>41</sup> Another study using a different CGP test (FoundationOne), which has both liquid biopsy- and tissue biopsy-based assays, reported a cost of \$4,700 per sample in 2021.<sup>42</sup> In the US, certain commercially available CGP tests require blood samples to be sent to central laboratories for analysis, and the results are reported to the donor's health care provider. One of these tests (Guardant360) costs US\$5,000 for people paying out-of-pocket.<sup>43</sup>

## Summary of the Evidence

We aimed to review randomized comparative studies that assess the diagnostic accuracy, clinical effectiveness, and cost-effectiveness of CGP tests compared with conventional molecular tests. However, given the emerging nature of the technology, no randomized controlled trials (RCTs) were identified. Similarly, the literature search for a recent systematic review examining CGP tests for NSCLC did not find any RCTs.<sup>44</sup> The authors of the systematic review indicated that for many people with advanced cancers for whom targeted therapies may be an option, logistical and ethical issues may limit the prospect for randomized trials.<sup>44</sup> Therefore, in most of these cases, evidence to assess the value of the technology is from real-world and non-randomized studies.

For this Horizon Scan, we present a summary of findings from systematic reviews and non-randomized studies that describe some of the emerging evidence about the detection capability of CGP technologies and their association with clinical outcomes, and economic studies assessing or modelling the value of CGP for health systems. The majority of studies identified relate specifically to CGP use in NSCLC. The use of CGP in other cancer types remains highly uncertain. This Horizon Scan report is not a systematic review of the evidence, the studies included were not critically appraised, and it does not endorse any information, diagnostic test, or technology.

### Detection Capability of CGP

Studies assessing CGP detection capability report a variety of different measures. These can include concordance rates (agreement of results between tests), number of actionable mutations identified, and the number of other mutations detected. Our search identified mostly validation studies without comparison groups or non-randomized studies comparing liquid- and tissue-based CGP tests among specific cancer types. We found published validation studies specific to the FoundationOne<sup>45,46</sup> and Guardant360<sup>47</sup> CGP tests. Also, a few studies that directly compared CGP with standard-of-care, and tissue-based, single-gene assays were identified.

Emerging evidence indicates that commercially available liquid-based CGP tests have high concordance with tissue-based CGP. For example, concordance of key actionable genes has been reported to be 93% for advanced prostate cancer,<sup>48</sup> 91% for colorectal cancer,<sup>49</sup> and 78% for NSCLC.<sup>50</sup> One prospective study using a CGP test for NSCLC found that adding liquid biopsy-based testing in combination with standard-of-care tissue-based genotyping identified 48% additional people (from 60 to 89) with actionable mutations.<sup>51</sup> A review examining NGS technology (not specific to CGP) reported that concordance rates compared

with single-gene testing were between 70% to 99% for NSCLC.<sup>31</sup> Evidence from primary studies and systematic reviews also indicated that although liquid-based tests can detect actionable mutations, tissue-based tests generally have higher sensitivity and detection capability.<sup>26,29,52-55</sup> Tissue-based tests provide higher quality genetic signals if the tumour can be accessed appropriately.

Several studies also report that the detection capability of liquid biopsy-based CGP tests can be limited when ctDNA concentrations are low due to tumour stage, cancer type, previous treatment or when there are other challenges to obtaining sufficient DNA.<sup>44,49</sup> A lack of detectable ctDNA or cfDNA overall within liquid biopsies may contribute to a higher rate of unsuccessful sequencing runs.<sup>56,57</sup> However, liquid-based CGP may be able to detect a higher rate of resistance mutations or signs of clonal hematopoiesis (mutations in stem cells that may or may not be linked to the tumour) among different cancers.<sup>29,48,58</sup> In 1 study of 1,288 people, liquid biopsy-based CGP led to a 65% increase in detecting driver mutations among people with NSCLC who were also tested with tissue-based assays.<sup>59</sup>

CGP may be better at detecting global mutation changes, such as tumour mutation burden, and characterizing tumour heterogeneity, which may not be possible with tissue-based assays that sample a fixed site of a tumour.<sup>30,60,61</sup> Detecting these additional mutations may have implications for informing treatment decisions and informing cancer prognoses. Ongoing assessment of liquid-based CGP tests, used alone or to complement standard tissue-based assays, can help inform whether they can reliably and accurately inform clinical decision-making in different contexts.

## Clinical Effectiveness

When assessing the clinical effectiveness of specific CGP tests or technology, consideration must be given to whether there are corresponding targeted therapies available for a particular condition and whether those therapies are associated with improved outcomes. Thus, identifying potentially relevant mutations with CGP testing may be used with other aspects of clinical decision-making and patient preferences in assessing whether awareness about mutations leads to treatment changes. Although some emerging evidence is available, in the absence of any identified randomized trials, the evidence about the specific use of liquid biopsy-based CGP tests (or liquid biopsy overall) and their clinical effectiveness is currently limited and uncertain.

A systematic review examining CGP tests (both liquid- and tissue-based) for NSCLC identified 17 non-randomized studies assessing clinical outcomes and reported it was not possible to pool an overall effect estimate of clinical effectiveness.<sup>44</sup> However, the authors stated that the emerging evidence indirectly supported the use of CGP tests as companion diagnostics because most studies that used the technologies reported improvements in clinical outcomes, such as relapse-free survival and overall survival, compared with historical control samples.<sup>44</sup>

Non-randomized comparison studies that directly compared liquid-based CGP to tissue-based CGP or to standard-of-care testing did not find liquid CGP was associated with significantly different clinical outcomes. These studies included a retrospective study of people with NSCLC who received either liquid biopsy-based CGP testing and/or tissue biopsy-based CGP.<sup>55</sup> The study found that a similar proportion of people were identified with actionable mutations and the progression-free survival rate was similar in those who received targeted therapies following the tests (liquid CGP: 13.8 months; tissue CGP: 10.6

months).<sup>55</sup> A prospective study reported that using targeted therapies after liquid CGP for NSCLC was not associated with inferior clinical outcomes compared with standard-of-care tissue-based testing (statistical comparisons were not possible due to overlapping groups).<sup>62</sup> One study examined the use of a liquid biopsy–based CGP at a single centre for a variety of cancers, including lung, breast, pancreatic, and colorectal cancers.<sup>63</sup> The authors noted that participants in the study were heavily pre-treated (with a median of 3 prior lines of systemic therapy), which made it difficult to draw meaningful conclusions about comparative benefits. However, they stated that it would be preferable to provide precision-based therapies in early-stage disease.<sup>63</sup> Although further research is needed, findings from these emerging studies suggest that liquid-based CGP clinical performance is not inferior to other tests used in routine care.

Identifying relevant mutations could inform clinical trial eligibility and may be associated with other secondary outcomes. For example, 1 study reported that CGP technologies may help recruitment for biomarker-based clinical trials for a variety of cancers.<sup>29</sup> CGP technologies could also support care of people with cancers of unknown primary origin because they could improve diagnosis and inform targeted therapy.<sup>64</sup> Overall, further research is needed to assess different CGP assays and whether they are associated with improved clinical outcomes and/or other non-clinical benefits compared with single-biomarker assays.<sup>6</sup>

## Economic Evidence

CGP technology is rapidly evolving; however, there is uncertainty about its clinical effectiveness and applicability for different cancers.<sup>40</sup> A useful cost-effectiveness analysis to inform pan-Canadian decision-makers about genetic testing may need a framework or a standardized approach. In the absence of both elements, it will be difficult to conduct a credible cost-effectiveness analysis that will influence CGP uptake.<sup>9</sup> Although, the emerging economic evidence remains uncertain, we summarize some of the key findings from economic reviews<sup>31,40,65</sup> and budget impact studies about CGP and similar NGS technologies focused on Canadian jurisdictions.<sup>9,27,66</sup>

Reviews have highlighted challenges in assessing the economic evidence for CGP and other NGS tests because there are varied comparators used across studies. For example, CGP may be compared with single-biomarker assays, serial testing, or no genetic testing in different situations.<sup>40</sup> Describing an overall cost-effectiveness without common comparators is complex and challenging. CGP technologies may also reveal secondary findings that could have clinical importance later on, but may be difficult to track over time and may not have been reported in studies.<sup>40</sup> Identifying specific actionable mutations may also not necessarily lead to treatment changes because treatment decisions are influenced by varied clinical practice, patient-related factors, and other considerations not directly linked to specific test results.<sup>65</sup> Other factors that make estimating the cost of CGP technologies challenging include the cost of corresponding therapies and the variety in sequencing technologies, infrastructure, and miscellaneous aspects.<sup>40,65</sup>

One narrative review examined the economic evidence comparing NGS with single-biomarker assays (10 studies) and the evidence comparing liquid biopsies to tissue biopsies (3 studies) for NSCLC.<sup>31</sup> The review reported mixed findings; some studies reported cost savings with NGS compared to serial single-biomarker assays, while other studies indicated NGS may be associated with minimal cost increases.<sup>31</sup> The review suggested that NGS-based assays may be cost-effective compared with single-biomarker assays if they can help identify better treatments or additional people who may be eligible for targeted therapies.<sup>31</sup> However,

another review reported that, as of yet, studies comparing NGS to single-biomarker assays have not shown significantly different survival outcomes for people with NSCLC.<sup>65</sup> A US-based cost-effectiveness modelling study that assessed CGP and multi-gene panel testing (not NGS) to no tumour profiling found neither testing technologies were cost-effective but were associated with additional life-years gained compared with no tumour profiling.<sup>67</sup> Both types of testing technologies exceeded the willingness-to-pay threshold (US\$150,000 per quality-adjusted life-year) in the model.<sup>67</sup> The prices of targeted therapies had a large influence on costs in the model, and the authors indicated that the results would likely be different in other countries with different pricing structures.<sup>67</sup> The narrative review also reported that liquid biopsies tend to have faster turnaround times and may be less costly per patient than tissue biopsies, but exact costs would depend on how liquid-based tests were used in different contexts (e.g., as a triage test or alone).<sup>31</sup>

A budget impact analysis of using a specific CGP technology for NSCLC in Ontario modelled 4 scenarios.<sup>9</sup> These scenarios had decreasing use of CGP and ranged from scenario 1, in which CGP would replace all single-gene assays upfront, to scenario 4, in which liquid-based CGP would be limited to specific people who cannot be assessed by a tissue biopsy. The study estimated an incidence of 5,109 people per year with NSCLC who could be eligible for testing and assumed a 50% uptake for the province.<sup>9</sup> In the models, all scenarios were associated with a budget increase and an increase in added life-years. Over a 3-year period, the cost of scenario 1 was estimated to be \$37.1 million and the cost of scenario 4 was estimated to be \$4.4 million.<sup>9</sup> Scenario 1 was associated with an increase in 680.9 life-years and scenario 4 with an increase of 132.1 life-years compared with single-gene testing.<sup>9</sup> The study modelled the broad budget impact of introducing the testing technology and did not estimate the impact of testing as part of different treatment models.<sup>9</sup> Another study assessed the budget impact of a situation similar to scenario 4, (where tissue biopsy may not be feasible) and estimated that the 3-year cost of CGP testing across Canada to be \$14.7 million with a projected 168 additional life-years.<sup>27</sup> Further economic evaluations considering specific case uses of CGP and broader implications on health systems will help improve understanding the technology's cost-effectiveness. To help inform health systems in Canada, economic assessments may need to consider the technology's potential uses for cancers other than NSCLC in the future.

## Who Might Benefit?

Most of the emerging evidence about CGP is related to NSCLC because it has a high number of potential diagnostic and therapeutic biomarkers.<sup>19</sup> More than 29,000 people are diagnosed with lung cancer each year in Canada, and it accounts for more cancer deaths than other major cancers combined (approximately 21,000 annually).<sup>68,69</sup> NSCLC is the most common form of lung cancer, accounting for 80% to 85% of all cases.<sup>19,70</sup> The specific incidence of NSCLC in Canada was not identified, and the number of people who may be eligible for CGP would depend on clinical need and suitability.

Health care professionals considering using CGP would need to take into account the proportion of people diagnosed with a particular type of cancer who may have actionable mutations, the availability of therapies targeting those mutations, and whether CGP is a better alternative to conventional testing.<sup>18</sup> For some people, additional information that may be provided by liquid biopsy-based CGP, such as tumour mutation burden or tumour

heterogeneity, may be more important to guide their treatment.<sup>30</sup> In addition to NSCLC, colorectal, ovarian, and some blood cancers have a high number of actionable mutations and may be more likely to benefit from CGP testing if there are corresponding targeted therapies available.<sup>8</sup>

## Issues to Consider

### Testing Infrastructure

Should health systems use CGP — or, more broadly, NGS technology — as part of routine care, it will likely require a shift in the locations where testing is performed. Conventional PCR-based assays or immunological tests are performed within most hospital settings.<sup>6</sup> However, NGS technology requires more sophisticated equipment, specialized training, and a higher volume of samples (batch testing) for efficiency. The upfront resource requirements for both wet lab (sample preparation) and dry lab (data analysis) are also greater for NGS than conventional testing.<sup>6</sup> For NGS technologies to be more widely adopted, centralized models of testing may need to be considered. Currently, most of the infrastructure for NGS is limited to academic or research-based clinical settings rather than community hospitals.<sup>2</sup> In a more centralized model of testing, liquid or tissue samples could be collected at community hospitals and sent to designated centres for analysis. Although certain community sites could also receive the necessary equipment and training, it may take time to collect the volume of samples needed to run sequencing with this testing method, which could result in delays compared with conventional testing.<sup>6</sup> In a centralized model, quality assurance of samples collected at different sites should be monitored to ensure sample preparation and handling to not affect the DNA content, quality, and subsequent analysis.<sup>30</sup>

A review of genetic services in Ontario stated that centralized genetics testing could improve coordination and administration of testing technologies.<sup>71</sup> Centralized models could expand NGS availability beyond academic centres, with important implications for equity as access to the technology improves regardless of where patients receive their cancer care.<sup>2,71</sup> A survey has shown that stakeholders involved in precision medicine across Canada similarly support the development of centralized systems for testing and co-assessment of tests and corresponding drugs to improve efficiency and reduce duplication of effort across jurisdictions.<sup>22</sup> Stakeholders also reported a need for greater regulatory oversight of testing technologies and transparency about laboratory-developed tests.<sup>22</sup>

NGS tests can generate a substantial amount of data that require an appropriate infrastructure for storage, security, and privacy protection.<sup>26</sup> Such protections and oversight may be more feasibly developed within centralized centres rather than local laboratories. A review of NGS technologies indicated that there may be an unmet need for appropriate data infrastructure and bioinformatics expertise in Canada.<sup>16</sup> A study describing Norway's experiences piloting liquid biopsy-based NGS testing (including CGP) highlighted that the rapidly changing technology can make it difficult to select and prioritize technologies for adoption.<sup>72</sup> Therefore, along with infrastructure development, a centralized testing model may require a shift in processes related to purchasing decisions for specific tests. It is likely that more targeted therapies will continue to emerge with parallel innovations in testing technologies. Should centralized models be adopted, enhanced processes for reviewing the

clinical and cost-effectiveness of emerging targeted therapies, corresponding companion diagnostics, and approaches for managing testing administration will likely be required.<sup>6</sup>

## Interpreting Complex Results

Some CGP tests are capable of characterizing hundreds of genes, measuring tumour mutational burden and other genomic information. Single-gene assays remain the most commonly used approach, and most targeted therapies are currently designed based on the profile of a single biomarker.<sup>6,7</sup> However, within routine care, CGP could reveal mutations across multiple genes. Therefore, if emerging therapies were to be used across a wider mutational profile, the interpretation of CGP-derived mutation data could become much more complex for health care professionals.<sup>6</sup> This information could be important for understanding whether different mutations interact to affect therapeutic response or indicate the likelihood of developing drug resistance. Clinical guidelines may not go into granular details about all position mutations and would require interpretation by individual providers or clinical teams.<sup>8</sup> In addition to genomic changes, and because liquid biopsies can be used to assess circulating tumour cells and other cellular components found in plasma or other fluids, emerging technologies could provide multiple layers of information that would require further interpretation.<sup>33</sup> Integrating and interpreting of the complex information could disrupt traditional approaches for clinical decision-making. Approaches using artificial intelligence are increasingly being considered and incorporated into precision medicine and may be used to support decision-making.<sup>6</sup>

Health care professionals would ultimately need to translate that information for their patients. Two studies, from the US<sup>73</sup> and Australia,<sup>74</sup> examined the perceptions of oncologists in interpreting genomic profiling information. Participants in both studies revealed that although they felt confident in their understanding of testing, using results to inform treatments, and explaining the technology to patients, they reported less confidence in interpreting more complex findings or information about secondary mutations.<sup>73,74</sup> Oncologists also reported that they would benefit from receiving additional training about interpreting tests results and communicating more complex findings to patients.<sup>73,74</sup> Increased recruitment and additional training for health care professionals specializing in genetics (including oncologists and genetic counsellors) have been recommended in Canada as demand for genetic services continues to increase.<sup>71</sup>

## Understanding Patients' Perspectives

CGP tests that use liquid biopsy based on fluid samples, such as blood, and are minimally invasive and more accessible than tissue biopsy-based tests. Patients with cancer have reported they are more likely to prefer liquid biopsies than tissue biopsies, if the technology can provide similar information to guide treatment decisions.<sup>75</sup> In cases in which tissue biopsy is not feasible, liquid biopsy-based CGPs could provide an alternative to people for whom there were no previous options.<sup>9</sup> A study that surveyed people who underwent genomic profiling reported that most overwhelmingly favoured testing if it provides an opportunity to receive tailored treatment and avoid adverse effects of non-targeted therapies that could be less effective.<sup>76</sup>

One systematic review of studies that assessed people's psychosocial outcomes for cancer genetic testing identified 22 eligible studies for a range of different cancers, but found that most studies assessed experiences of people being tested for hereditary cancers.<sup>77</sup> The authors of the review found that people who received testing specifically for treatment

selection or disease monitoring generally valued genomic testing because they felt it provided a sense of empowerment, reduced uncertainty, and could help with better treatment options.<sup>77</sup> Negative experiences were reported by people with identified mutations without available targeted therapies.<sup>77</sup>

Another review on patients' and oncologists' expectations about using NGS for cancer profiling highlighted the importance of educational resources that clearly explain what testing entails and how results could be used to inform care.<sup>78</sup> In particular, information should be provided about data privacy, secondary findings, and potential implications of results such as hereditary mutations for family members.<sup>8,71,78</sup> Improving patient and family education about testing and the interpretation of findings has been recommended by clinical experts.<sup>8,71</sup> Ongoing engagement of diverse patient groups about their experiences and expectations of new and emerging genomics technology will be important to inform their use.<sup>79</sup>

## Final Remarks

Should emerging evidence indicate a clear benefit of CGP testing, it could be an opportunity to facilitate greater integration of precision medicine within routine cancer care. In contrast to conventional molecular assays, such as PCR, that are often targeted to a specific cancer type and single biomarker, CGP can characterize hundreds of genes and other genetic elements. A single CGP test could be used to inform multiple treatment options across different cancers, which would change the paradigm of existing companion diagnostic tests in which a single test informs the use of single drug. In addition, liquid biopsy–based CGP technologies could provide alternatives for people for whom tissue-based testing may not be feasible and could provide additional information about therapeutic options and prognoses.<sup>6</sup> However, currently, the vast majority of biomarker profiles are associated with NSCLC, for which clinical practice guidelines recommend broad-based genomic testing.<sup>37,38</sup> For most other types of cancer, the number of actionable biomarkers or genes that can inform treatment selection is currently limited.<sup>18</sup> Whether the use of CGP can provide additional benefits over conventional molecular testing across different cancer types, remains uncertain at this time and needs more assessment.<sup>2,6</sup> Because CGP is based on NGS-based technology, the upfront costs of specialized equipment, data analysis, technical training, and other required components would affect health systems' budgetary allocations.<sup>9,31</sup> The emerging evidence is also not yet well-established to determine if the technology confers significantly better clinical outcomes to make it cost-effective.<sup>40,44</sup> There are no RCTs on CGP at this time, probably due to feasibility constraints. Therefore, non-randomized studies and real-world experiences will continue to be important evidence sources. Should evidence reviews, cost-effectiveness studies, and clinical guidelines demonstrate substantial value of CGP and other NGS technologies over standard testing protocols in Canada, health systems may need to factor in related issues, such as testing infrastructure and increased training of health care professionals to interpret and use test results, as part of adoption considerations.

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