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Context
Biomarkers are physiological indicators that can be measured and used to assess a person’s health.1 Cancer biomarkers may be used to detect, diagnose, or manage certain types of cancer. These biomarkers include versions of genes known to be associated with cancer, or proteins that are present or elevated in persons with cancer.2 Examples of cancer biomarker testing include:

- testing for anaplastic lymphoma kinase gene rearrangements or epidermal growth factor receptor mutation analysis to determine the treatment and prognosis of non–small cell lung cancer2
- BCR-ABL gene testing to diagnose and monitor the status of chronic myeloid leukemia2
- estrogen receptor and progesterone receptor testing to determine hormone therapy treatments for breast cancer2
- human epidermal growth factor receptor 2 (HER2)/neu testing to determine whether to treat breast, gastric, and esophageal cancers with trastuzumab.2

Information is being sought on the safeguards, accreditation, training, and standards in place for cancer biomarker testing across Canada. There is an interest in developing strategies for quality assessment for biomarker testing, specifically for the following testing methodologies: immunohistochemistry (IHC), in situ hybridization (ISH), fluorescence in situ hybridization (FISH), polymerase chain reaction, and genomic sequencing.

Objective
The objective of this Environmental Scan is to identify and summarize information regarding cancer biomarker testing in Canada. The following questions are addressed:

1. What are the quality assurance and accreditation requirements for cancer biomarker testing in each Canadian jurisdiction?
2. What is the association between the quality of laboratory test results for cancer biomarkers and the laboratory experience and volume of testing?
Methods
The findings of this Environmental Scan are based on responses to the Cancer Biomarker Testing in Canada 2015 survey (Appendix 1) and a limited literature search. To identify the quality assurance and accreditation requirements for cancer biomarker testing (Question 1), surveys were sent to key informants from cancer agencies and health care agencies from jurisdictions across Canada. Survey data were gathered until September 23, 2015. To identify the association between the quality of laboratory test results and the experience or volume of the laboratory (Question 2), a limited literature search was conducted on key resources including MEDLINE, Embase, PubMed, and the Cochrane Library. Grey literature was identified using the CADTH Grey Matters checklist. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, and guidelines. Where possible, retrieval was limited to the human population. The search was limited to English-language documents published between January 1, 2010 and August 13, 2015. Conference abstracts were excluded from the search results.

Quality assurance measures and accreditation requirements for cancer biomarker testing in Canadian jurisdictions is the focus of this report. Quality assurance measures for laboratory medicine in general, and specific requirements for each accreditation program, were considered out of the scope of this report.

Findings
Surveys were distributed to contacts in all ten provinces. Multiple surveys were sent to each jurisdiction. Surveys were not sent to the territories (Northwest Territories, Yukon, and Nunavut), as cancer biomarker testing is not performed in these jurisdictions. Survey responses were received from informants in Alberta, British Columbia (BC), Manitoba, New Brunswick, Nova Scotia, Ontario, and Prince Edward Island (PEI) — one response per province (Appendix 2). Survey responses were not received from Saskatchewan, Newfoundland and Labrador, and Quebec. Stakeholder feedback was used to supplement information retrieved from the survey respondents.

Quality Assurance for Cancer Biomarker Testing
Quality assurance includes measures taken to minimize errors and ensure a minimum standard of performance in laboratory testing. Survey respondents were asked about quality assurance measures in their jurisdictions regarding testing for cancer biomarkers.

Of the survey responses received, all have quality assurance requirements for cancer biomarker testing. An overview of the methods for quality assurance in each jurisdiction based on responses from the Cancer Biomarker Testing in Canada 2015 survey (Section A) is reported in Table 1.
Table 1: Quality Assurance for Cancer Biomarker Testing in Canada

<table>
<thead>
<tr>
<th>Jurisdiction</th>
<th>Quality Assurance Methods</th>
</tr>
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</table>
| Alberta          | • Provincial Quality Management System  
• Document management and control  
• EQA including external accreditation by CAP, UK NEQAS, and cIQc  
• IQA including audits and reviews  
• Proficiency testing  
• Equipment management, calibration, maintenance, and decommissioning  
• Documentation on training and competencies of laboratory personnel  
• Provincial Anatomical Pathology Quality Assurance Plan, including technical requirements for sample testing  
• Best practices–sharing amongst laboratories in the jurisdiction |
| BC               | • SOPs  
• Document control and management for quality and technical records  
• Quality manual  
• Equipment records, maintenance, and calibration  
• EQA cIQc, UK NEQAS, and NordiQC  
• IQC and internal audits  
• Proficiency testing  
• Instrument validation  
• Management review  
• Medical peer review  
• Methodology validation  
• Non-conformities review  
• Procedures and templates for result reporting  
• Risk identification  
• Technical requirements for sample testing |
| Manitoba         | • SOPs  
• Document management and control  
• Quality management  
• EQA  
• IQC  
• CAP proficiency testing  
• Method and instrument validation  
• Equipment maintenance  
• Technical requirements for sample testing |
| New Brunswick    | • SOPs  
• Document management and control  
• Quality manual  
• Equipment calibration and maintenance  
• CAP EQA  
• IQC  
• Method and instrument validation  
• Clinical correlation (i.e., are findings what we would expect given the clinical presentation of the patient?) |
Alberta
In Alberta, a limited number of laboratories, primarily located in Edmonton and Calgary, perform the majority of cancer biomarker testing. Three large laboratories perform molecular testing for cancer. In both Edmonton and Calgary, there is one large IHC laboratory where ISH testing is also performed; in each city, there is one distinct laboratory where the majority of the FISH testing for cancer patients is performed. These laboratories coordinate testing and share best practices with the smaller centres across the province. Laboratories are also required to follow the Provincial Anatomical Pathology Quality Assurance Plan.

British Columbia
In BC, laboratories at the BC Cancer Agency and a limited number of public health authority laboratories perform IHC, ISH, and polymerase chain reaction-based testing for cancer biomarkers. In BC, no private facilities perform cancer biomarker testing. All laboratories adhere to requirements mandated by the Diagnostic Accreditation Program (DAP).

Manitoba
Public laboratories in Manitoba (operated through Diagnostic Services Manitoba) perform IHC at all sites and ISH at a limited number of sites. Private laboratories in Manitoba do not typically perform complex testing, such as IHC or ISH, for cancer biomarkers. However, public laboratories in Manitoba provide access for the private sector to HER2 and estrogen receptor/progesterone receptor IHC testing. All testing adheres to the College of American Pathologists requirements.
New Brunswick
In New Brunswick, individual public laboratories determine the scope of testing performed. In the province, no private laboratories perform cancer biomarker testing. There are also no reference laboratories.

Nova Scotia
In Nova Scotia, one public laboratory performs cancer biomarker testing. Laboratories participate in an accreditation cycle, as a legal basis for quality assurance requirements for cancer biomarker testing.

Ontario
Standards for laboratories licensed by the Ministry of Health and Long-Term Care exist for performing cancer biomarker testing, although the specific quality assurance measures in place may vary by laboratory.

Prince Edward Island
Cancer biomarker testing in PEI is centralized through a provincial laboratory at the Queen Elizabeth Hospital in Charlottetown. There are no private laboratories in the province.

Accreditation Requirements for Cancer Biomarker Testing
Participation in formal accreditation requirements, as specified by external organizations, can be a component of quality assurance; and in turn, requirements for accreditation may require specific quality assurance measures — such as those outlined in Table 1 — to be met. In addition to questions about quality assurance in general, survey participants were asked about specific accreditation requirements in their jurisdictions.

According to the survey responses, all seven responding jurisdictions have specific accreditation requirements (in addition to the quality assurance measures already in place) for cancer biomarker testing. The type of and legal basis for accreditation requirements vary by jurisdiction.

PEI requires both laboratory facilities and physicians to be accredited, whereas accreditation is required for facilities only in Alberta, BC, Manitoba, New Brunswick, Nova Scotia, and Ontario.

Physicians and laboratory facilities in PEI are accredited through Accreditation Canada,\textsuperscript{9} this is a voluntary process.

Laboratory facilities in Alberta are accredited by the College of Physicians & Surgeons of Alberta.\textsuperscript{10} Both private and public laboratories in Alberta adhere to provincial testing policies (i.e., Alberta’s Quality Management System and related documents) to ensure standardization to meet accreditation requirements. Accreditation standards are reviewed by the College of Physicians and Surgeons of Alberta on an ongoing basis, and formal reviews occur on an annual basis. The provincial government mandates that laboratories in Alberta be accredited and the Provincial Quality Management System ensures that laboratories adhere to these requirements.

In BC, laboratory facilities are accredited by DAP.\textsuperscript{8} There is no difference in accreditation standards for public, specialized, or reference laboratories. Participation in a four-year accreditation cycle is required. Failure to participate in accreditation cycles results in withdrawing services from laboratories. For laboratories to add services (e.g., IHC testing), an initial assessment of the laboratory is performed by DAP, and services are not permitted to commence until all DAP requirements are
fulfilled. Laboratories are also required to have medical peer review programs that require the participation of physicians. Physicians providing pathology services must be licensed by the College of Physicians and Surgeons of British Columbia, and are only permitted to perform services within their licensed scope.

Manitoba uses the College of American Pathologists and Manitoba Quality Assurance Program accreditation programs for their laboratories.

In Ontario, adherence to the regulatory standards of the Institute for Quality Management in Healthcare (IQMH; formerly Ontario Laboratory Accreditation) is required for government-issued licences for accreditation. Laboratories may participate in accreditation cycles — a process of regular review for accreditation purposes to ensure quality assurance requirements.

Laboratories in New Brunswick are accredited through the IQMH. In the province, public laboratories participate in an accreditation cycle as a legal basis for quality assurance requirements for cancer biomarker testing.

Nova Scotia is currently in the process of obtaining voluntary IQMH accreditation. Nova Scotia also participates in Accreditation Canada processes for laboratory accreditation.

**Quality, Volume, and Experience in Laboratory Testing, and Their Association**

The literature search identified evidence regarding the association between the quality of lab test results for cancer biomarkers and the experience and volume of the lab. The aim was to assess external factors that may affect the quality of the testing rather than to confirm the validity or diagnostic accuracy of the individual tests.

**Experience of Laboratory Personnel**

Molecular pathology is a quickly changing field; continuing education for pathologists is therefore recommended in order that they develop and maintain their competencies. This is especially relevant for the interpretation of test results, which can be complex and require expertise. There is a significant emphasis on the importance of laboratories participating in external quality assessment (EQA) programs, especially for IHC testing, and the role of EQA in the education of technicians and pathologists. EQA programs can identify laboratories performing poorly and may be able to provide targeted technical training or advice. Continuous communication between laboratories, to achieve optimum IHC results, is also recommended. For FISH testing, the following were identified as requirements for quality assurance: EQA, internal quality assessment (IQA), and competent personnel, in addition to test and instrument validation.

The American Society of Clinical Oncology and the College of American Pathologists guideline for IHC testing of ER/PR in breast cancer recommends that laboratory personnel competency testing be mandated by the director of each facility, and be in accordance with the Clinical Laboratory Improvement Amendments. The guideline also recommends that competencies be documented and audited on a regular basis. This recommendation was supported by the survey responses for this Environmental Scan (Question 1), which indicated that documenting training and competencies of technical staff is part of ensuring quality assurance of cancer biomarker testing in Canada.

Thus, personnel competence was identified as an important component of ensuring high-quality cancer biomarker testing. Continuous education and participation in EQA programs were identified as ways to ensure personnel proficiencies.
Volume of Testing

Regarding molecular cancer pathology testing in general, a recent guidance document by the European Society of Pathology Task Force on Quality Assurance in Molecular Pathology and the Royal College of Pathologists states that the volume of samples needed for a laboratory to be considered reliable has more to do with the feasibility and cost-effectiveness of providing testing than any threshold value. This guidance document does not recommend providing testing services (such as testing for HER2) if the number of patients is small (no threshold number of patients specified). The reasons for this recommendation are based on cost-effectiveness rather than clinical reliability.

One Canadian study assessed the association of quality of IHC performance and laboratory experience with volume of testing. Seventy-two laboratories across Canada participated from 2008 to 2011 and performed IHC testing on both breast and non-breast cancer markers. Thirty-two academic laboratories (laboratories associated with an anatomic pathology residency program at a teaching hospital and regarded as centres of excellence) and 40 non-academic laboratories participated. Of the 72 laboratories, 47 were large city laboratories (population greater than or equal to 300,000) and 25 were small city laboratories (populations of less than 300,000). A laboratory was either a non-academic centre or an academic centre, and was either located in a small or large city. Participating laboratories also reported on approximate numbers of IHC tests performed per year (i.e., less than 5,000; 5,000 to 10,000; greater than 10,000 to 30,000; greater than 30,000 to 50,000; and greater than 50,000). This study did not find a statistically significant difference in IHC performance for academic centres versus non-academic centres, or between large city laboratories versus small city laboratories. There was no statistically significant difference based on volume alone. However, the authors cautioned that a certain degree of competency is needed to perform IHC testing and to interpret results, but that this competency is not limited to one type of centre.

Requirements for being a reference laboratory vary across regions and are based on the type of testing. Requirements may also be different depending on how the results will be used. The National Comprehensive Cancer Network stipulates that if the results of testing will inform patient care decisions, then the laboratory must be certified by the Clinical Laboratory Improvement Amendments (requirements in the US and which Canadian laboratories may follow). However, if the results of testing are to be used for research, the laboratory does not require certification. Guidelines and recommendations by the Canadian Association of Pathologists state that large centres are not automatic candidates for reference laboratories for molecular testing in general, but that certain proficiencies must be met (i.e., individual laboratories should attain 95% or better concordance with a reference laboratory or reference method to be deemed a reference laboratory; and should attain 90% concordance with a reference laboratory to obtain testing certification). This organization recommends that instead of volume of testing, a threshold value of proficiency testing must be met. The Canadian Immunohistochemistry Quality Control program has enumerated other criteria for a laboratory to be considered a reference laboratory for ER/PR IHC testing, which includes: staining corresponding to clinical and patient outcomes; large volume of IHC testing; longstanding record of IQA; and successful participation in EQA. The specific volume of IHC testing was not specified.

The evidence regarding the volume of testing needed to maintain testing proficiency is limited. Guidelines from the Canadian National Consensus Meeting on HER2/neu testing in breast cancer recommends that IHC testing be carried out in laboratories that perform at least 250 IHC tests annually and recommends that FISH testing be carried out in laboratories that perform at least 100 FISH tests annually.
factors, such as participation in IQA and EQA, as well as cost-effectiveness and feasibility, may need to be considered for the establishment of reference laboratories.

Limitations
The findings of this Environmental Scan are intended to present an overview of the current status of cancer biomarker testing in Canada rather than a comprehensive review of the topic. The findings of this report are based on a limited literature search and survey responses from a limited number of jurisdictions. Although multiple surveys were sent to each jurisdiction, only one response per province was received. Therefore, the report may not provide a complete representation of all Canadian jurisdictions, as some respondents were only able to speak to a limited number of laboratories in their jurisdiction. Survey responses and information regarding quality assurance and accreditation requirements for cancer biomarker testing were not provided by three provinces and therefore practices in Saskatchewan, Newfoundland and Labrador, and Quebec are uncertain. The responses received provided a general overview of the requirements for quality assurance measures and accreditation, thus information on the legal basis for each individual measure in Table 1 is uncertain (i.e., information on whether certain measures were voluntary or mandatory was not provided). Findings from the literature search are limited. Included guidelines provided limited information regarding volume of testing and specific competencies for laboratory experience.

Conclusion
Cancer biomarker testing is important for the detection, diagnosis, or management of certain types of cancer. This Environmental Scan reports current aspects of cancer biomarker testing in Canada. Both a survey and a literature search component were used to assess quality assurance and accreditation for cancer biomarker testing.

Survey responses were received from seven provinces: Alberta, BC, Manitoba, New Brunswick, Nova Scotia, Ontario, and PEI. Many methods for quality assurance for cancer biomarker testing were identified across Canadian jurisdictions and include participation in EQA and IQA, equipment management, standard operating procedures, laboratory accreditation through external accreditation agencies, and best practices—sharing amongst laboratories. All seven responding jurisdictions have specific accreditation requirements for cancer biomarker testing. According to survey responses, laboratories performing cancer biomarker testing in Canada are accredited through the College of American Pathologists4 (Manitoba and PEI), Diagnostic Accreditation Program5 (BC), IQMH12 (Nova Scotia, New Brunswick, and Ontario), Manitoba Quality Assurance Program (Manitoba), Accreditation Canada9 (PEI and Nova Scotia), and the College of Physicians & Surgeons of Alberta10 (Alberta). The legal basis for accreditation varies for different jurisdictions.

The experience of laboratory personnel conducting cancer biomarker testing is an important aspect of quality assurance. Continuous education and participation in EQA programs were identified as ways to ensure personnel proficiencies. Guidelines from the Canadian Association of Pathologists exist around the volume of cases needed for laboratories to perform testing; however, these may be based on factors other than technical proficiencies, such as feasibility and cost-effectiveness. Several organizations have outlined requirements for the establishments of reference laboratories, which include personnel competencies and volume of testing performed.
References


Appendix 1: Cancer Biomarker Testing in Canada 2015 Survey

A. Quality Assurance for Cancer Biomarker Testing

1. Have quality assurance requirements for cancer biomarker testing been implemented in your jurisdiction? (If no, please proceed to question 5.)
   - YES  - NO

2. If yes, please outline the specific indicators used for quality assurance of cancer biomarker testing (i.e., standard operating procedure, document control, quality manual, maintenance/calibration, internal audits, external quality assessment, internal quality control, proficiency testing, validation of instruments and methods).

3. How are these indicators applied consistently across your jurisdiction? Is there a difference between private and public labs? Is there a difference between different categories of labs (e.g., specialized labs, reference labs)?

4. What is the legal basis for these quality assurance requirements for cancer biomarker testing (e.g., voluntary, government-issued licence, participation in accreditation cycle)?

5. If no, are there plans in development to address quality assurance requirements for cancer biomarker testing? (If yes, please complete Question 6.)
   - YES  - NO

6. When are these plans likely to be executed?
### B. Accreditation Requirements for Cancer Biomarker Testing

7. Have specific accreditation requirements for cancer biomarker testing been implemented in your jurisdiction? (If no, please proceed to Question 12.)
   - [ ] YES
   - [ ] NO

8. If yes, what is accredited: facilities, physicians, or both?
   - [ ] Facilities
   - [ ] Physicians
   - [ ] Both

9. Which accreditation scheme is used? (e.g., College of American Pathologists, Clinical Laboratory Improvement Amendments, Ontario Laboratory Accreditation, Accreditation Canada, other?)

10. What is the legal basis for accreditation (e.g., voluntary, government-issued licence, participation in accreditation cycle)?

11. Is accreditation applied consistently across the jurisdiction? Is there a difference between private and public labs? Is there a difference between different categories of labs (e.g., specialized labs, reference labs)?

12. If no, are there plans in development for accreditation requirements for cancer biomarker testing? (If yes, please complete Question 13.)
   - [ ] YES
   - [ ] NO

13. When are these plans likely to be executed?
## Appendix 2: Information on Survey Respondents

<table>
<thead>
<tr>
<th>Province</th>
<th>Organization Represented by Survey Respondents</th>
</tr>
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<tbody>
<tr>
<td>Alberta</td>
<td>Alberta Health Services</td>
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<td>BC Cancer Agency</td>
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<td>Diagnostic Services Manitoba</td>
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<td>Réseau de santé Vitalité</td>
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