



# Benefits, issues, and recommendations for personalized medicine in oncology in Canada

*C. Butts MD,\* S. Kamel-Reid PhD,<sup>†</sup> G. Batist MD,<sup>‡</sup>  
S. Chia MD,<sup>§</sup> C. Blanke MD,<sup>||</sup> M. Moore MD,<sup>#</sup>  
M.B. Sawyer MD,\* C. Desjardins PhD,\*\* A. Dubois PhD,\*\*  
J. Pun MSc MBA,<sup>††</sup> K. Bonter MSc,\*\* and F.D. Ashbury PhD<sup>‡‡</sup>*

## ABSTRACT

The burden of cancer for Canadian citizens and society is large. New technologies have the potential to increase the use of genetic information in clinical decision-making, furthering prevention, surveillance, and safer, more effective drug therapies for cancer patients. Personalized medicine can have different meanings to different people. The context for personalized medicine in the present paper is genetic testing, which offers the promise of refining treatment decisions for those diagnosed with chronic and life-threatening illnesses. Personalized medicine and genetic characterization of tumours can also give direction to the development of novel drugs. Genetic testing will increasingly become an essential part of clinical decision-making.

In Canada, provinces are responsible for health care, and most have unique policies and programs in place to address cancer control. The result is inconsistency in access to and delivery of therapies and other interventions, beyond the differences expected because of demographic factors and clinical education. Inconsistencies arising from differences in resources, policy, and application of evidence-informed personalized cancer medicine exacerbate patient access to appropriate testing and quality care. Geographic variations in cancer incidence and mortality rates in Canada—with the Atlantic provinces and Quebec having higher rates, and British Columbia having the lowest rates—are well documented.

Our purpose here is to provide an understanding of current and future applications of personalized medicine in oncology, to highlight the benefits of personalized medicine for patients, and to describe issues and opportunities for improvement in the coordination of personalized medicine in Canada. Efficient and more rapid adoption of personalized medicine in oncology in Canada could help overcome those issues and improve cancer prevention and care. That task might benefit from the creation

of a National Genetics Advisory Panel that would review research and provide recommendations on tests for funding or reimbursement, guidelines, service delivery models, laboratory quality assurance, education, and communication. More has to be known about the current state of personalized cancer medicine in Canada, and strategies have to be developed to inform and improve understanding and appropriate coordination and delivery. Our hope is that the perspectives emphasized in this paper will stimulate discussion and further research to create a more informed response.

## KEY WORDS

Personalized medicine, genetic testing, practice, quality, patient care, policy, guidelines

## 1. INTRODUCTION

Cancer has profound effects on individuals and society. According to recent estimates, 187,600 new cases of cancer and 75,500 cancer deaths occurred in Canada in 2013<sup>1</sup>. Nearly 1 in 4 Canadians will die from some form of cancer, the leading cause of premature death in Canada. Cancer is a complex disease, with many different phenotypes and genetic characteristics that define each specific tumour.

In addition to the personal toll incurred by a diagnosis of cancer, cancer imposes a large economic burden on Canadian society. Although current data are not available, the economic burden of cancer in 1998 was estimated to be \$14.2 billion in health care services and lost productivity<sup>2</sup>, a number that is certainly significantly higher today.

Provinces are responsible for health care, and most have unique policies and programs in place to address cancer control. The result is inconsistency in access to and delivery of therapies and other interventions to support the patient. Geographic variations in cancer incidence and mortality rates in Canada—with the Atlantic provinces and Quebec

having higher rates, and British Columbia having the lowest rates—are well documented<sup>1</sup>.

The burden of cancer for Canadian citizens and society is clear. Nevertheless, we are in an exciting time in which new opportunities are available to help mitigate the impact of cancer. New technologies have the potential to increase the use of genetic information in clinical decision-making, furthering prevention, surveillance, and safer, more effective drug therapies. Personalized medicine—in this context, genetic testing—promises to help refine treatment decisions for individuals diagnosed with chronic and life-threatening illnesses. Personalized medicine and genetic characterization of tumours can also help to direct the development of novel drugs. Genetic testing will increasingly become an essential part of clinical decision-making and, as such, will require appropriate coordination for effective adoption and delivery.

Genetic profiling of tumours is changing the cancer therapy paradigm. Although treatment based on organ of origin (breast, prostate, colon) will remain important for the foreseeable future, the genetic profile of a tumour and its microenvironment—for example, positivity for human epidermal growth factor receptor-2 (HER2), C-kit, or epidermal growth factor receptor (EGFR); negative for Kirsten rat sarcoma viral oncogene (*KRAS*), and so on—will refine disease prognosis in some cases and, more importantly, determine which treatments might be available, with predictive potential, to specific patients. We envision a day when patient and physician will have easy access to integrated and comprehensive patient data, including genetic information. Electronic tools at the point of care will help guide which tests can be ordered, will provide timely results and interpretation, and will provide information for patients and physicians to facilitate decision-making. Personalizing medicine based on genetic information should be supported by a national oversight body that establishes national policies, guidelines, funding recommendations, and best practices for testing and laboratory standards.

Genetic testing is also being used to predict cancer risk. Testing for mutations in the *BRCA* genes predicts risk of breast and ovarian cancers<sup>3</sup>. Also, numerous types of colorectal cancer (CRC) are inherited syndromes: for example, Lynch syndrome, familial adenomatous polyposis<sup>4</sup>, hereditary nonpolyposis CRC<sup>5</sup>. By identifying genetic changes in carriers, the risk of developing colon cancer can be assessed, and appropriate monitoring can be implemented.

## 2. WHAT IS PERSONALIZED MEDICINE IN ONCOLOGY IN CANADA?

Personalized medicine in oncology encompasses a variety of approaches. The implementation of genetic testing has led not only to prediction of an

individual's risk of developing a specific type of cancer (*BRCA* gene mutations, hereditary CRC), but has also permitted assessment of an individual's polymorphisms in the key enzymes involved in metabolizing cancer drugs such as tamoxifen and irinotecan (“pharmacogenomics”). Pharmacogenomics offers the opportunity to avoid severe toxicity in patients unable to adequately metabolize certain cytotoxic drugs or potentially to adjust the drug dose to improve efficacy or reduce toxicity.

Genetic tests can be characterized as prognostic or predictive, or both<sup>6</sup>. A prognostic test provides information about a baseline patient or tumour characteristic that can affect the outcome (“natural history”) of the cancer, regardless of treatment. A useful prognostic test might allow patients to be classified at low risk of relapse or death, therefore avoiding potentially toxic treatment, or at high risk and more likely to benefit from additional treatment. A predictive test identifies a baseline patient or tumour characteristic that suggests whether a patient is more or less likely to benefit from a specific treatment or intervention. A useful predictive test might allow therapy to be personalized for a patient based on the likelihood of benefit from the selected therapy.

The purpose of the present paper is to provide an understanding of current and future applications of personalized medicine in oncology and to highlight the benefit to patients. The main focus is genetic testing as it relates to treatment, including specific examples of how testing is used in Canada today. We also describe issues affecting delivery and coordination of personalized medicine in Canada and provide recommendations to help address those issues.

Since the early 1990s, knowledge of the genetic basis of cancer, coupled with rapid development of new technologies, has led to an increased understanding of the heterogeneity of cancer and an ability to develop new therapies targeting specific molecular pathways that may be driving a particular tumour's growth. Consequently, the concept of personalized therapy has evolved from selection of a treatment based on the various toxicity profiles of relatively equivalent therapies to selection of a specific treatment based on the genetic and molecular aspects particular to an individual patient's cancer. However, those targeted or specific treatments require that the tumour be pre-screened for the target in question—hence, the term “companion diagnostic” for the new genetic tests coupled to novel targeted drugs. Results of the genetic tests—that is, positivity (or not) for the presence of the target—determines the patients who are more likely or less likely to benefit and, hence, who will or will not receive the new treatment.

Although the new targeted cancer therapies undoubtedly offer the best treatment option, these agents can be very expensive (in the range of hundreds of thousands of dollars per patient), requiring a high bar based on economics for making the decision

to treat. Jurisdictions will need to determine if they will rely wholly on economic evaluation or on health policy that has economic policy as a key underpinning. Furthermore, the requirement for a companion diagnostic test raises a number of important issues such as the handling of disjointed approval and funding processes for the target drug and companion test, access to the companion test, and quality assurance in testing.

One of the most well-known examples of a targeted therapy in cancer is trastuzumab for the treatment of breast cancer, which started in 1999. The HER2 protein is overexpressed in 18%–23% of breast cancers and is associated with increased disease recurrence and poor prognosis. Treatment of breast cancer with the HER2-targeted antibody trastuzumab has been directed using fluorescence *in situ* hybridization (FISH) to profile amplification of the *ERBB2* gene (which encodes HER2), or immunohistochemistry (IHC) to profile HER2 protein expression<sup>7</sup>. In combination with chemotherapy, trastuzumab has improved progression-free and overall survival in patients with both operable early-stage<sup>8</sup> and metastatic breast cancer<sup>9</sup>, representing a significant benefit for 18%–23% of the 20,000 Canadian women diagnosed with breast cancer annually.

Studies of HER2 testing in breast cancer patients between 1999 and 2002, in Canada and elsewhere, showed that quality control and standardization of testing were needed<sup>10</sup> and indicated that IHC testing alone may not be reliable or accurate in identifying patients who might benefit from trastuzumab<sup>11</sup>. Between 2003 and 2005, the use of IHC, with validation by FISH for equivocal IHC results, was established as a reliable and accurate approach<sup>11–13</sup>. In 2007, Canadian practice guidelines for HER2 testing in breast cancer were published, recommending the use of both IHC and FISH<sup>14</sup>. Based on Canadian data, the cost-effectiveness of this approach was also established<sup>15</sup>. Because of well-documented issues with the reliability of HER2 IHC testing<sup>16</sup>, the Canadian Immunohistochemistry Quality Control Program was established and made available to all Canadian labs in 2009<sup>17</sup>. The program provides a proficiency testing program for IHC testing and was recently shown to facilitate accurate and reproducible HER2 testing as part of routine practice<sup>18</sup>.

Another example of targeted therapy is imatinib for the treatment of chronic myeloid leukemia. Chronic myeloid leukemia is caused by a somatic mutation that results in formation of the Philadelphia chromosome, which in turn generates a mutant gene called *BCR-ABL* (breakpoint cluster region–Abelson murine leukemia viral oncogene homolog 1). Imatinib specifically binds to the Bcr-Abl protein and inhibits its role in uncontrolled cell proliferation. Great benefit to patient outcomes has been shown when cytogenetic techniques (to identify the Philadelphia chromosome) and genetic techniques (to

identify the mutant Bcr-Abl transcript) are used to determine whether imatinib treatment is warranted and to monitor treatment efficacy<sup>19</sup>.

Colorectal cancer affects more than 21,000 Canadians annually. Outcomes in metastatic CRC (mCRC) have improved because of the availability of new cytotoxic agents and targeted agents. Cetuximab and panitumumab are monoclonal antibodies targeting EGFR. Randomized trials<sup>20,21</sup> have shown improved outcomes in patients with mCRC treated with those agents, both of which have been marketed in Canada since 2008. Still, up to 50% of mCRC patients do not respond to these therapies and hence might be subjected to toxicity with no benefit. Although the target for these agents is EGFR, lack of benefit has been shown to be a result of mutations in *KRAS*, a gene that codes for a protein downstream of EGFR<sup>22,23</sup>. By screening mCRC tumours for *KRAS* mutation status before treatment with expensive antibody therapy, unnecessary toxicities and costs can be avoided in individuals who are unlikely to respond<sup>24</sup>. As this application of genetic testing to screening demonstrates, the use of such tests can greatly contribute to health system sustainability through cost reduction.

In 2009, the U.S. National Comprehensive Cancer Network and the American Society of Clinical Oncology (ASCO) strongly recommended *KRAS* testing for all mCRC patients before use of anti-EGFR antibody therapy<sup>25</sup>. Canadian practice guidelines and recommendations were published later<sup>26</sup>, as was a 2010 Ontario Health Technology Advisory Committee analysis, which concluded that *KRAS* testing is both beneficial and cost-effective for Canadians<sup>27</sup>.

Despite Health Canada approval of both cetuximab and panitumumab (with reimbursement for those drugs in some provinces starting in 2008), no public funding or Canadian strategy was initially established to make *KRAS* testing available to all Canadians who might benefit. As a result, funding and provision of testing were initially arranged through the drug manufacturers (Amgen and Bristol–Myers Squibb)<sup>28</sup>. Today, *KRAS* funding is increasingly being assumed by the provinces. This type of model is more desirable and sustainable in the long term.

Identification of molecular targets and development of drugs for those targets have a very significant impact on drug development and approval, in terms of potential access to therapeutics. One example is genetic testing for mutations in *BRAF* (v-raf murine sarcoma viral oncogene homolog B1) that are associated with short progression-free and overall survival in malignant melanoma. The *BRAF* gene codes for a kinase that is downstream of *KRAS* and targeted by the selective inhibitor vemurafenib. In combination with *BRAF* genotyping, vemurafenib represents a major advance in melanoma treatment. It is effective in reducing tumour size by up to 50%, and it extends progression-free survival in 40%–60% of patients who have tumours that harbour the V600E



*BRAF* mutation<sup>23</sup>. Another example is the identification of activating mutations or translocations in the *ALK* (anaplastic lymphoma kinase) gene. Originally described in anaplastic large-cell lymphoma<sup>29</sup>, *ALK* mutations have also been found in 2%–7% of non-small-cell lung cancer (NSCLC) cases<sup>30</sup>. In NSCLC, a translocation of the *EML4* gene with *ALK* results in a fusion gene encoding for a protein with constitutive kinase activity. This translocation appears to define a molecular subgroup of NSCLC that is susceptible to targeted kinase inhibition. Crizotinib is an oral selective inhibitor of *ALK* and *MET* tyrosine kinases. A two-part phase I trial of crizotinib in patients with NSCLC carrying *ALK* rearrangements, almost 60% of whom had received at least two prior lines of therapy, found that crizotinib resulted in a 57% objective response rate, with 87% of patients experiencing disease control at 8 weeks<sup>31</sup>. In an update reported at the ASCO annual meeting in 2011, Shaw *et al.*<sup>32</sup> reported a 2-year survival of 64%, with median overall survival not yet reached. Recent research presented at the 2012 ASCO meeting reported promising results for children with *ALK*-driven tumours treated with crizotinib<sup>33</sup>.

Vemurafenib and crizotinib both went from promising phase I trials to randomized phase III trials, thus considerably shortening the usual clinical drug development timeline. These agents and their companion diagnostic tests were all recently approved by the U.S. Food and Drug Administration. Crizotinib received accelerated approval based on two promising single-arm trials. These examples demonstrate how identification of molecular targets has affected drug development and approval and the subsequent identification and selection of specific patient populations for access.

The ability to use molecular and genetic testing to define patient subgroups with high response rates in phase I trials raises important issues for phase III trials. Some authors have argued that, in disease settings lacking effective therapies, randomized trials comparing an agent having a high response rate with a placebo would be unethical or at least unacceptable to patients and clinicians<sup>34</sup> and that standards should therefore be flexible to allow for accelerated approval of new targeted agents after impressive phase I and II results.

An example of a personalized medicine test that provides prognostic information (the ability to estimate the likelihood of an outcome) and that can inform treatment choice is the commercially available Oncotype DX test (Genomic Health, Redwood City, CA, U.S.A.). The test provides a recurrence score based on a mathematical algorithm of the expression of 16 genes (and 5 control genes) in breast tumour tissue. In a subpopulation of breast cancer patients, recurrence scores can be used to identify individuals with a low risk of disease recurrence<sup>35</sup> who may not derive significant benefit from adjuvant chemotherapy. Patients who are at low risk

and who choose to forgo chemotherapy can avoid the associated toxicities, side effects, and direct and indirect expenses. The American Society of Clinical Oncology and the National Comprehensive Cancer Network guidelines have recommended the use of Oncotype DX since 2007, and costs for the test are reimbursed by most U.S. private insurance companies. The Ontario Health Technology Advisory Committee recommended Oncotype DX for use in newly diagnosed node-negative estrogen-receptor-positive patients in 2010, with a provision for collecting data on the actual use of the test information<sup>36</sup>. Before 2009, access to Oncotype DX testing in Canada was largely restricted to patients participating in clinical trials<sup>37</sup>. In early 2010, testing was funded by the Ministry of Health and Long-Term Care in Ontario through its out-of-country funding program. But even with that funding, only 962 Canadians were tested in 2010<sup>38</sup>, and it is estimated that as many as 10,000 Canadian women annually meet the ASCO, National Comprehensive Cancer Network, or Ontario Health Technology Advisory Committee criteria for testing. The associated reduction in chemotherapy could reduce net health care system expenditures by \$12–\$35 million depending on the percentage of patients who choose to forgo chemotherapy<sup>36,38</sup>. Identifying the most appropriate testing options is important, and it is therefore anticipated that additional research into other genetic tests will help to ensure that physicians and patients are offered the most appropriate and cost-effective test to inform decision-making.

### 3. ISSUES IN ONCOLOGY PERSONALIZED MEDICINE IN CANADA

Successful implementation of genetic testing in oncology faces serious challenges. Those challenges include the need for additional regulated oversight of laboratories and quality assurance programs, processes and structures to approve tests for use, and specific funding for genetic tests. The issues are multifaceted and negatively affect access to testing, quality of testing, and ability to offer interventions that improve patient outcomes. Failure to appropriately address these issues will only exacerbate current national and provincial inequities in education and training for personalized genetic testing, coordination of hospital and laboratory resources for testing, patient access to personalized genetic testing and quality of care in the absence of appropriate testing, and as more such tests emerge, a missed opportunity to provide better health care.

#### 3.1 Quality Assurance

Access to reliable high-quality genetic testing is essential to maximize the benefit that can be derived from new and existing practices in personalized

medicine for individuals, subpopulations, and the health care system. Reliability and quality of testing can be assured through an effective regulatory framework for clinical laboratory operations, medical testing, and diagnostic devices. Tests are provided as a laboratory service by hospitals or private companies and are subject to provincial regulations related to laboratory operations, accreditation, and quality control. The regulatory framework varies significantly from province to province<sup>40</sup>, and national oversight or guidelines to facilitate harmonization and good practice in all provinces is lacking<sup>39</sup>.

Recent experience and publications have addressed the reliability of estrogen receptor testing in situations in which regulation to ensure quality may be insufficient. A recent inquiry into estrogen receptor testing practices in Newfoundland and Labrador revealed that, when retested in a central laboratory in Ontario, approximately one third of 1023 estrogen receptor tests performed on patients in that Canadian province between 1997 and 2005 had been falsely scored negative. The inquiry revealed that errors occurred because of laboratory staff turnover and lack of relevant training for pathologists and technologists to perform the testing, lack of appropriate quality assurance methods, inadequate quality control policies and practices, and poor communication and teamwork among health care professionals<sup>41</sup>.

### 3.2 Processes to Evaluate and Recommend Genetic Tests

In Canada, decisions to approve genetic tests for funding are made at the provincial level. Some provinces have no process in place to review and approve genetic tests, nor established mechanisms to implement test use. Among the provinces that have processes to evaluate genetic tests for funding, the processes differ. For example, some provincial oncology programs have formed their own committees to evaluate proposed genetic tests and to make recommendations to the relevant provincial government. However, the criteria used by some provincial ministries of health to evaluate such recommendations are either absent or vague. Some provinces have evaluation-focused organizations and initiatives; however, those organizations are not mandated, nor do they communicate with each other to ensure equity and consistency across the country. Nationally focused leadership organizations and initiatives across the country currently include the Canadian Standards Association, Accreditation Canada, and the National Standards Committee of the Canadian Association of Pathologists. One or more of these organizations may be able to help lead a national effort to standardize the process for evaluating and recommending genetic tests.

Without formal provincial processes in place to evaluate new tests and technologies, individual

hospitals are under increasing pressure from physicians and patients to make decisions and to offer every new genetic test. Some hospital laboratories have implemented independent reviews of clinical data and the published literature to evaluate whether a test is clinically appropriate. If the result of the review indicates support for the test, the hospital laboratory then has to assess the costs and resources necessary to offer the test. These independent hospital-based decisions result in considerable duplication of effort, a lack of standards, and inequities in the tests being made available across institutions, contributing to public and provider confusion. Moreover, it is sometimes unclear which hospitals are offering which genetic tests. Some hospital laboratories may offer to conduct tests for other hospitals that do not perform the test, but it is unclear how willingness and capacity to perform the tests are communicated and decided on, and also whether a fee-for-service structure is in place (which may also result in inequitable access).

### 3.3 Funding for Specific Genetic Testing

All hospital laboratories in Canada receive fixed provincial funding to support their operations. Any 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. To offer a new genetic test, hospital laboratories must often redirect existing funds (for example, reduce funding of other services to fund the new test) or obtain funding from other sources (for example, from the hospital department requesting the test). Also, provincial ministries of health do not typically provide funding for other testing-related activities, including proficiency evaluation, staff training, and development of new testing protocols. Some provinces provide specific funding for certain designated tests (for example, HER2 FISH in Ontario), but why those tests receive “special” funding status compared with other tests funded through hospital budgets is not clear.

Currently, two genetic tests (*KRAS* and *EGFR*) have received funding in one province (Alberta) and funding support from pharmaceutical companies. The investment by pharmaceutical companies is predicated on the notion that the costs of testing will be recovered when new patients who will be candidates to use their therapeutics are identified. A positive view of this situation is that government funds the tests and hospital budgets are not used. By contrast, industry funding might stop when the specific drug receives funding approval, or access to the tests might be limited by virtue of providing testing only when a patient qualifies for the therapy. This option is not sustainable because of its unpredictable reliance on pharmaceutical industry involvement. Indeed, it is reasonable to assume that industry is expecting to

recover its costs based on models that have estimated the numbers of patients who will benefit; otherwise, they would not facilitate access to the drugs.

#### 4. RECOMMENDATIONS FOR A PAN-CANADIAN FRAMEWORK FOR PERSONALIZED MEDICINE IN ONCOLOGY

To summarize, key challenges to the implementation of personalized medicine in oncology in Canada are

- lack of consistent quality assurance and regulated laboratory oversight both nationally and provincially;
- inconsistent or nonexistent processes to assess and approve genetic tests for use and to determine what the standard of care should be; and
- lack of public funding at the provincial level for specific genetic tests linked to therapeutics.

As noted earlier, there are best practice programs scattered around the country, but the lack of consistency and national coverage are problematic. Together, those issues limit physician access to information about appropriate testing, and individuals with knowledge may experience challenges in adopting and adapting that knowledge within their local environment in the absence of supportive policies and structures, further exacerbating inequalities in access for patients. As a result of those challenges, we suggest the creation of a National Genetics Advisory Panel with appropriate structures, policies, and processes to lead the country and its provinces and territories into the era of personalized medicine.

##### 4.1 A National Genetics Advisory Panel

Canada and the provinces and territories must make fundamental changes in how genetic testing is managed and how decisions are made to approve or delist genetic tests. A pan-Canadian approach to quality improvement in health care has recently been recommended<sup>42</sup>. There are numerous examples of similar frameworks: the Public Health Agency of Canada's National Advisory Committee on Immunization; the Pan-Canadian Oncology Drug Review Program, which was created to assess oncology drugs and to provide recommendations to the provinces and territories (excluding Quebec) about which cancer drugs they should fund under their public drug programs; and the Common Drug Review at the Canadian Agency for Drugs and Technologies in Health. Perhaps a similar national approach is necessary to reduce intra- and interprovincial inequities in funding, access, and delivery, while increasing and improving the quality of genetic testing services and care.

The proposed National Genetics Advisory Panel could provide recommendations to the provinces and territories to ensure evidenced-based, timely, and

consistent clinical data analysis and interpretation about the use of new genetic tests. Those recommendations would help to establish appropriate financial parameters for funding by delineating requirements for appropriate application of tests. The panel should include pan-Canadian, multidisciplinary representation (in oncology, laboratory genetics, and health economics) and should leverage existing provincial strengths across the country. Pan-Canadian representation would also help to align provincial strategies and policies for personalized cancer medicine and potentially address access through careful articulation of requirements for use within provincial boundaries. The panel would also liaise with provincial agencies to provide advice that local organizations would use in their respective jurisdictions to implement genetic testing, reflecting consistency in interpretation and ensuring quality in the application of tests. Although the National Genetics Advisory Panel could adopt various organizational structures, certain essential roles and functions that should be present are described next, in greater detail.

##### 4.2 Oversight and Funding or Reimbursement Recommendations

An expert oversight committee should oversee the activities of various subcommittees and be responsible for various aspects of genetic testing in oncology. Because funding or reimbursement for genetic testing is a critical challenge in Canada, the oversight committee would be responsible for recommending the tests that provinces should fund (or delist), including developing an appropriate cost model for each test as a benchmark for provinces to measure against their own implementation of the test. Funding recommendations from a credible national body, with provincial adoption of the recommendations, would help to avoid the current situation of access inequities for patients and reliance on pharmaceutical company programs to support test funding.

##### 4.3 Review of Research Evidence, and Testing Recommendations

A subcommittee focused on reviewing literature and scanning in-depth for new genetic tests would ensure rapid and efficient adoption of new practices and maximize benefits to Canadians. This subcommittee should have close ties to the research community, holding regular meetings to discuss and anticipate future genetic testing technologies and their potential relevance to oncology patients. There are currently groups in Canada that conduct these time-intensive reviews, and the subcommittee should link and integrate with those groups. In the context of new oncology therapeutics, the subcommittee should recommend the type of genetic test to be used as a companion diagnostic—for example, FISH or polymerase chain reaction. The



resulting information, which would include economic data, would be used to produce national recommendations for tests that have clinical validity and utility and that should be implemented across the country. Finally, once a test is approved and used in Canada, this subcommittee would also continue to evaluate and review existing tests, determining if they continue to be appropriate.

#### 4.4 Development of Guidelines and Service Delivery Models

After recommendations for funding and implementing new genetic tests have been developed, guidelines and service delivery models should also be developed that provide consistent standards for provinces and territories to follow. This paper has highlighted serious issues that can arise if appropriate guidelines are not implemented and adopted. Where guidelines already exist, their implementation is inconsistent across provinces. Guidelines for effective implementation and service delivery of genetic tests should include roles for various professions (genetic counsellors, clinical geneticists, oncologists, laboratory staff), definitions of the target population, tissue sample standards, standard operating procedures for laboratories, quality standards, testing algorithms, proficiency testing requirements, and appropriate training and credentials for staff who perform genetic testing. Service delivery model recommendations should also include recommendations on how to implement laboratory service logistics such as minimum volumes and guidelines that ensure quality and cost effectiveness. There is also a need for classification of genetic tests based on complexity and patient risk, which would help to illuminate the level of review required for various tests. Classification should also include recommendations about the minimum volume of tests required to warrant performing a test in a specific laboratory.

#### 4.5 Laboratory Quality Assurance

Another key function required to ensure the highest level of accuracy in testing is a means for accreditation and regular inspection of laboratories that perform genetic tests. It should include 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. The quality assurance program would assist laboratories in the implementation of quality systems (or augment existing systems) and provide a harmonized and standardized approach for genetics labs across Canada. A subcommittee on laboratory quality assurance should also eventually integrate with Accreditation Canada's external peer review program to promote and sustain a quality improvement culture in the country's genetic testing laboratories. In some provinces, a high

level of expertise and valuable testing infrastructure is already available. That expertise and infrastructure can be leveraged and shared to promote efficiencies on both the national and provincial levels.

#### 4.6 Education and Communication

Educating physicians and other health care professionals on the benefits, challenges, and most importantly, the clinical utility of genetic testing in oncology is a needed critical task in Canada<sup>43</sup>. A subcommittee of the National Genetics Advisory Panel should help to integrate new curriculum into education programs for health professionals and to lead continuing education in genetic testing across Canada. Finally, there should be credible nationally coordinated efforts to communicate the benefits, risks, and challenges of genetic testing. With providers and the public as audiences, this subcommittee would have the role of developing the strategy, tactics, and key messages relating to genetic tests that would provide a trusted voice on issues concerning personalized medicine. The United States currently has a Molecular Genetics in Pathology subspecialty program, which could be considered in Canada to evaluate the extent to which the training programs offered are appropriate at a pan-Canadian level.

Although important, education is insufficient to ensure the appropriate use of approved genetic testing in practice. Education and communication will need to be supported by monitoring and evaluation of test implementation. Quality assurance programs at the institutional level will need to gather and report data on implementation by providers to ensure that all eligible patients are tested and that the results of tests have been used to inform decision-making.

### 5. CONCLUDING REMARKS

A number of specific issues related to regulated laboratory oversight, lack of process (for assessing, approving, and delisting genetic tests for use), and lack of provincial funding for specific genetic tests prevent efficient and equitable adoption of beneficial genetic testing practices in Canada. We recommend establishing a National Genetics Advisory Panel to work with the provinces and existing organizations to promote evidence-based, timely, and consistent adoption and practice of genetic testing in Canada. The proposed roles and functions of this Advisory Panel are oversight, funding or reimbursement recommendations, review of research evidence and testing recommendations, development of guidelines and service delivery models, laboratory quality assurance, education, and communication. This type of structure currently exists in other jurisdictions—for example, the Evaluation of Genomic Applications in Practice and Prevention Initiative in the United States (<http://www.egapreviews.org/>) and EuroGentest in

the European Union (<http://www.eurogentest.org/>)—and could be leveraged in establishing a Canadian solution. By providing leadership, assuring access to high-quality testing nationally, and enabling effective evaluation, adoption, reimbursement, and practice, the panel can, we believe, realize the full benefits of personalized medicine for all Canadians and for the health care system, with applications across many medical disciplines.

More needs to be known about the current state of personalized cancer medicine in Canada, and strategies must be developed to inform and improve understanding and appropriate coordination and delivery. Our hope is that the perspective emphasized in this paper will stimulate discussion and further research to create a more informed response.

## 6. ACKNOWLEDGMENTS

The authors thank Drs. Jean Deschenes, Aly Kar-san, Anthony Magliocco, Denis Soulières, and Alan Spatz, and Ms. Line Pelosse.

## 7. CONFLICT OF INTEREST DISCLOSURES

No financial conflict of interest exists for any author with respect to this paper.

## 8. REFERENCES

- Canadian Cancer Society's Steering Committee on Cancer Statistics. *Canadian Cancer Statistics 2013*. Toronto, ON: Canadian Cancer Society; 2013.
- Canadian Cancer Society and the National Cancer Institute of Canada. *Canadian Cancer Statistics 2004*. Toronto, ON: Canadian Cancer Society; 2004.
- Gronwald J, Tung N, Foulkes WD, *et al.* on behalf of the Hereditary Breast Cancer Clinical Study Group. Tamoxifen and contralateral breast cancer in *BRCA1* and *BRCA2* carriers: an update. *Int J Cancer* 2006;118:2281–4.
- Jaspersion KW, Tuohy TM, Neklason DW, Burt RW. Hereditary and familial colon cancer. *Gastroenterology* 2010;138:2044–58.
- Gala M, Chung DC. Hereditary colon cancer syndromes. *Semin Oncol* 2011;38:490–9.
- Mehta S, Shelling A, Muthukaruppan A, *et al.* Predictive and prognostic molecular markers for cancer medicine. *Ther Adv Med Oncol* 2010;2:125–48.
- Wayne K, Sibbald B. Patient demand and politics push Herceptin forward. *CMAJ* 2005;173:347–8.
- Perez EA, Romond EH, Suman VJ, *et al.* Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2–positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol* 2011;29:3366–73.
- Slamon DJ, Leyland-Jones B, Shak S, *et al.* Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783–92.
- O'Malley FP, Thomson T, Julian J, *et al.* HER2 testing in a population-based study of patients with metastatic breast cancer treated with trastuzumab. *Arch Pathol Lab Med* 2008;132:61–5.
- Bartlett J, Mallon E, Cooke T. The clinical evaluation of HER-2 status: which test to use? *J Pathol* 2003;199:411–17.
- Hicks DG, Tubbs RR. Assessment of the HER2 status in breast cancer by fluorescence *in situ* hybridization: a technical review with interpretive guidelines. *Hum Pathol* 2005;36:250–61.
- Mass RD, Press MF, Anderson S, *et al.* Evaluation of clinical outcomes according to HER2 detection by fluorescence *in situ* hybridization in women with metastatic breast cancer treated with trastuzumab. *Clin Breast Cancer* 2005;6:240–6.
- Hanna W, O'Malley FP, Barnes P, *et al.* Updated recommendations from the Canadian National Consensus Meeting on HER2/neu testing in breast cancer. *Curr Oncol* 2007;14:149–53.
- Dendukuri N, Khetani K, McIsaac M, Brophy J. Testing for HER2-positive breast cancer: a systematic review and cost-effectiveness analysis. *CMAJ* 2007;176:1429–34.
- Seidenfeld J, Samsom DJ, Rothenberg BM, Bonnell CJ, Ziegler KM, Aronson N. HER2 testing to manage patients with breast cancer or other solid tumors. *Evid Rep Technol Assess (Full Rep)* 2008;1–362.
- Terry J, Torlakovic E, Trotter M, *et al.* Canadian external quality assurance program for breast cancer biomarkers. *Appl Immunohistochem Mol Morphol* 2010;18:486.
- Lu FI, Torlakovic EE, Makretsov N, *et al.* Human epidermal growth factor receptor 2 (HER2) immunohistochemistry: accurate and highly reproducible testing results among Canadian laboratories. *J Pathol* 2011;3:16–20.
- Vigil CE, Griffiths EA, Wang ES, Wetzler M. Interpretation of cytogenetic and molecular results in patients treated for CML. *Blood Rev* 2011;25:39–46.
- Amado RG, Wolf M, Peeters M, *et al.* Wild-type *KRAS* is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:1626–34.
- Cunningham D, Humblet Y, Siena S, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004;351:337–45.
- Khambata-Ford S, Garrett CR, Meropol NJ, *et al.* Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. *J Clin Oncol* 2007;25:3230–7.
- Siena S, Peeters M, Van Cutsem E, *et al.* Association of progression-free survival with patient-reported outcomes and survival: results from a randomised phase 3 trial of panitumumab. *Br J Cancer* 2007;97:1469–74.
- Soulières D, Greer W, Magliocco AM, *et al.* *KRAS* mutation testing in the treatment of metastatic colorectal cancer with anti-EGFR therapies. *Curr Oncol* 2010;17(suppl 1):S31–40.
- Allegra CJ, Jessup JM, Somerfield MR, *et al.* American Society of Clinical Oncology provisional clinical opinion: testing for *KRAS* gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. *J Clin Oncol* 2009;27:2091–6.
- Aubin F, Gill S, Burkes R, *et al.* Canadian Expert Group consensus recommendations: *KRAS* testing in colorectal cancer. *Curr Oncol* 2011;18:e180–4.



27. Health Quality Ontario. *KRAS* testing for anti-EGFR therapy in advanced colorectal cancer: an evidence-based and economic analysis. *Ont Health Technol Assess Ser* 2010;10:1–49.
28. Molecular Oncology Task Force. *Ensuring Access to High Quality Molecular Oncology Laboratory Testing and Clinical Cancer Genetic Services in Ontario*. Toronto, ON: Cancer Care Ontario; 2008.
29. Kutok JL, Aster JC. Molecular biology of anaplastic lymphoma kinase–positive anaplastic large-cell lymphoma. *J Clin Oncol* 2002;20:3691–702.
30. Soda M, Choi YL, Enomoto M, *et al*. Identification of the transforming *EML4-ALK* fusion gene in non-small-cell lung cancer. *Nature* 2007;448:561–6.
31. Kwak EL, Bang YJ, Camidge DR, *et al*. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med* 2010;363:1693–703.
32. Shaw AT, Yeap BY, Solomon BJ, *et al*. Impact of crizotinib on survival in patients with advanced, *ALK*-positive NSCLC compared with historical controls [abstract 7507]. *J Clin Oncol* 2011;29:. [Available online at: <http://meetinglibrary.asco.org/content/76959-102>; cited July 13, 2013]
33. Mosse YP, Balis FM, Lim MS, *et al*. Efficacy of crizotinib in children with relapsed/refractory *ALK*-driven tumors including anaplastic large cell lymphoma and neuroblastoma: a Children's Oncology Group phase I consortium study [abstract 9500]. *J Clin Oncol* 2012;30:. [Available online at: <http://meetinglibrary.asco.org/content/96905-114>; cited July 13, 2013]
34. Chabner BA. Early accelerated approval for highly targeted cancer drugs. *N Engl J Med* 2011;364:1087–9.
35. Habel LA, Shak S, Jacobs MK, *et al*. A population-based study of tumor gene expression and risk of breast cancer death among lymph node-negative patients. *Breast Cancer Res* 2006;8:R25.
36. Ontario Health Technology Advisory Committee. *Multi-gene Expression Profiling for Guiding Adjuvant Chemotherapy Decisions in Women with Early Breast Cancer*. Toronto, ON: Ontario Ministry of Health and Long-Term Care; 2010.
37. Ragaz J. The 21-gene assay and its impact on breast cancer treatment. *Oncol Exchange* 2010;9:6–8.
38. Ragaz J. The 21-gene assay: Canada's uneven response. In: Cancer Advocacy Coalition of Canada (CACC). *Report Card on Cancer in Canada, 2010–2011*. Toronto, ON: CACC; 2011: 41–3.
39. Petit É, Tassé AM, Godard B. An empirical analysis of the legal frameworks governing genetic services labs in Canadian provinces. *Health Law Review* 2008;16:65–72.
40. Li H, Adeli K. Laboratory quality regulations and accreditation standards in Canada. *Clin Biochem* 2009;42:249–55.
41. Hammond ME, Hayes DF, Dowsett M, *et al*. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med* 2010;134:e48–72.
42. Sullivan T, Ashbury FD, Pun J, Pitt BM, Stipich N, Neeson J. Responsibility for Canada's healthcare quality agenda: interviews with Canadian health leaders. *Healthc Pap* 2011;11:10–21.
43. Bonter K, Desjardins C, Currier N, Pun J, Ashbury FD. Personalised medicine in Canada: a survey of adoption and practice in oncology, cardiology and family medicine. *BMJ Open* 2011;1:e000110.

**Correspondence to:** Fredrick D. Ashbury, Intelligent Improvement Consultants, Inc., 10 Milner Business Court, 3rd floor, Toronto, Ontario M1B 3C6.  
**E-mail:** fashbury@intel-icon.com

- \* Department of Oncology, University of Alberta, Cross Cancer Institute, Edmonton, AB.
- † Department of Pathology, Division of Molecular Diagnostics, The University Health Network, Toronto, ON.
- ‡ Segal Cancer Centre, Jewish General Hospital, McGill University, QC.
- \$ Department of Medicine, University of British Columbia, BC Cancer Agency, Vancouver, BC.
- || Medical Oncology, Vancouver General Hospital and the University of British Columbia, and Systemic Therapy, BC Cancer Agency, Vancouver, BC.
- # Medical Oncology and Hematology, Princess Margaret Hospital, University Health Network, and Mount Sinai Hospital, Toronto, ON.
- \*\* Centre of Excellence in Personalised Medicine, Montreal, QC.
- †† Intelligent Improvement Consultants, Inc., Toronto, ON.
- ‡‡ Illawarra Health Medical Research Institute, University of Wollongong, NSW, Australia; Division of Preventive Oncology, University of Calgary, Calgary, AB; Department of Health Policy, Management and Evaluation, University of Toronto, and Intelligent Improvement Consultants, Inc., Toronto, ON.