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Canadian Breast Cancer Network
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PRECISION ONCOLOGY AND BREAST CANCER: CONSIDERING CANADA'S APPROACH IN AN EVOLVING LANDSCAPE

Patient and Clinician Perspectives and Recommendations on the Application and Integration of Genomically Guided Care in Breast Cancer

INTRODUCTION

The cancer treatment landscape is undergoing a seismic shift with the emergence and evolution of precision oncology approaches. With genomic profiling or testing, clinicians and patients can identify key drivers of a patient's cancerous tumour, which may better predict disease behaviour, in turn informing more precise treatment decisions. In addition to providing an expanded array of treatment options, a more targeted method can potentially reduce treatment toxicities, improve outcomes, and provide a better quality of life for patients. This approach seeks to deliver a more individualized treatment model, with the goal of matching the right drug to the right person at the right time.

The increasing availability and affordability of DNA sequencing[i] is accelerating opportunities for precision oncology programs around the world. In Canada, many centres have introduced genomic profiling for cancer in some capacity, but its use for breast cancer is not yet standard. Given certain therapies require confirmation of a biomarker, there are concerns about equitable access to testing, as well as testing turnaround times. In some instances, it can take weeks to months for results to be returned. The lack of a clear framework around when and who should be tested is generating many questions amongst patients and clinicians.

The promise of wide scale genomic testing is its potential to guide more targeted and effective treatment options and avoid those with less or no utility. This could offer significant cost savings and improve treatment outcomes by sparing the system unnecessary costly procedures and ineffective medications.[ii] The question remains what the federal government's role is (vs. provincial and territory leadership) in regulating and integrating genomic profiling nationally to ensure effective therapy and equitable access. National guidelines and funding protocols would help define and ensure equitable access for all cancer patients. It could also help determine which patients would benefit most, and at what point in their disease journey to test and possibly retest. Canada is not alone as other countries have yet to set forth clear frameworks.

Breast cancer is highly heterogeneous and increasingly, there is a shift from a single biomarker, single drug approach towards a series of more complex decisions. These decisions are guided by sequencing the genetic or molecular features of a cancer. Health Canada has already approved several targeted therapies that require testing for molecular biomarkers prior to use, including the recent approval for the first tumor-agnostic treatment for cancer [*See Appendix B*].

In terms of new therapies, even with these approvals, timely patient access remains a challenge. The current regulatory process can take between one to two years

depending on the therapy type[iii] and then up to another eight months for the funding decisions.[iv] Questions persist on how the system can best adapt to keep pace, especially with regards to evaluating rapidly evolving clinical data. Given how precise the new treatments are, there is a decrease in the feasibility for gold standard phase III randomized trials and an increased reliance on basket trials, phase II data and real world evidence (RWE) in their place.[v] In some situations, despite a positive Health Canada approval for use, a pattern of negative funding recommendations is emerging from the health technology assessment frameworks used to evaluate cancer drugs (pCODR and INESSS).[vi] Although the evaluation welcomes expert input, this is often overruled causing dismay within the oncological and patient community as new therapies are not made available. How can we more effectively straddle the difference in what's seen as clinically relevant and accepted endpoints between regulatory bodies? How can we ensure new and novel trial designs will be accepted? Are there learnings from the rapid approach to the COVID-19 vaccination approvals that can be applied to speed up approvals, in turn improving outcomes for those living with breast and other forms of cancer?

The rapid advancements being made in genomically driven disease management are bringing a tsunami of change to the Canadian healthcare system. Now is the time for Canada to set itself up for the successful integration of this evolving science. As decisions emerge around the regulation and implementation of both testing and treatment, it is critical they are informed by patient and physician values.

Breast cancer, as the most common malignancy and cause of cancer-associated death amongst women worldwide,[vii] is primed to be significantly impacted by these advancements. Given this, the Canadian Breast Cancer Network (CBCN) has been observing this transformation carefully in the early front runners such as non-small cell lung cancer, who have seen significant advances in disease management because of precision testing and new targeted treatments that deliver substantial clinic benefit to subsets of patients.

To help understand the different perspectives and values on precision oncology in breast cancer and the role of testing and data, the CBCN hosted two national virtual roundtables – one with breast cancer patients living with different types and stages of disease and one with oncologists. The following paper shares observations, key takeaways and recommendations based on insights collected from these conversations.

CURRENT UNDERSTANDING OF PRECISION MEDICINE AMONGST PATIENTS AND CLINICIANS

Given the newness and complexity of precision oncology, the patient group participated in an hour-long information session prior to their participation in the roundtable to provide unbiased, fact-based education about precision oncology, genomic profiling, actionable biomarkers, and the current Canadian landscape. Overall, six participants had little awareness of genomic profiling and the advancement of precision oncology. The one exception was a participant who was extremely informed on available testing, treatments and funding options available in Canada and beyond.

The clinician group included three medical oncologists and one surgical oncologist from across Canada. Given their expertise and research experience with precision oncology, the CBCN did not hold an education session ahead of the virtual roundtable. Several members of the group felt that the current utility of genomic profiling to guide treatment in breast cancer had been disappointing to date compared with other cancers. Participants did acknowledge this was in-part because breast cancer has already benefited from some very successful targeted therapies whose use is informed by standard protein-based biomarkers (or cytogenetics in the case of HER2-targeted therapies), and they expect the usefulness of testing is likely to increase as more therapies against actionable targets are developed and evaluated.

Both groups commented that there is inconsistent communication, education, and testing on genomic profiling. They agreed geography can be a key factor affecting this, among other things. For clinicians, eligibility for clinical trials is a significant, if not principal rationale for testing. However, those not affiliated with research hospitals and/or living outside urban centres have limited access to both testing and trials.

The key topics discussed at both roundtables included:

- Patient and physician values regarding communication and information on emerging precision oncology testing and treatments
- The role of testing and identification to determine which patients should be automatically considered for testing
- Creating an approval and funding process for both testing and treatments that is nimble and streamlined to handle a shift toward individualized treatment approaches

The Patient Perspective

During the patient roundtable the participants acknowledged they had a better understanding than the typical patient on the role of precision oncology in breast cancer. The following summarizes the three key take-aways that emerged from the session:

1. **Build confidence and understanding with accessible information and communication on precision oncology and genomic profiling**
   Every patient wants to feel confident that they are getting the best treatment to help treat their disease and improve quality of life. By proactively sharing more transparent, real knowledge on precision oncology, patients can make educated decisions in partnership with their healthcare team on the appropriate use of precision oncology and allay the fear of missing out. The group acknowledged the science is evolving quickly and it's not reasonable to expect that every doctor has every piece of information. They felt the creation of a reliable and easily accessible resource offering patients consistent, current information on precision medicine and its advances would help. They also felt doctors should proactively communicate why they would or would not benefit from a precision oncology approach (either for testing or treatment choice).

> *"There is so much jargon it can be intimidating and you're already dealing with being sick and then worried you're missing important information."*

2. **A need for equitable testing**
   By sharing their individual experiences, the group members perceived there to be disparities in access to current testing, therapies, and clinical trial opportunities. With significant differences depending on the patient's location and clinical team, the group was concerned that the requirement for testing in precision medicine would further magnify this inequity across the country. Recognizing that it may not be feasible or useful to test/retest everyone, the group felt strongly that there is an urgent need for a national framework to guide who would receive genomic profiling and when. Priority groups for consideration included people with metastatic disease as well as early-stage patients with BRCA mutations. They also felt regardless of available funding, patients should be made aware of genomic testing and why it may or may not be of benefit for them.

"It's very hard to make a blanket statement since cancer is very individualized. However, the options should be presented to everyone."

"Just because right now I don't have any mutations does not,mean that when it goes to my liver, I won't have a new mutation."

3. Alignment of the current regulatory process to support a more individualized treatment approach

There was much frustration within the patient group regarding the length of time and other perceived barriers in Health Canada's approval and the subsequent CADTH review process for new treatments. While they shared their respect for Canada's evidence-based rigour, the group wondered if "red-tape" could be reduced so that patients could access new therapies sooner. One example is rethinking how the drug approval process might be retooled to focus on specific biomarkers versus disease origin. Another pertains to acceptance of clinical data provided by trials such as basket trials and phase II data. The group called for more urgency for people with metastatic disease to have the "right to try" treatments even if this means the indication and/or funding status of an NOCc therapy may be cancelled based on additional RWE. The group referenced the changing indications on some COVID-19 vaccines based on RWE, and how that should be applied to oncology drug approvals too.

"Breast cancer patients are not one and the same. There must be room for individualized care where patients make informed decisions based on all available information."

Living a healthy life was the top priority uniting the patient group. They also expressed excitement at the prospect of more precise and individualized approaches that could improve survival and quality of life outcomes. Working in partnership with their health care providers, these women want to play an active role in controlling their fate. They identified the importance of having an evidence-based national framework for testing and other precision oncology tools to ensure equitable and consistent access no matter where a patient lives.

"It shouldn't matter that I'm dying from something that's not transmittable, it should matter that I'm dying."

The Physician Perspective

The physician roundtable also focused on the same themes as those discussed in the patient session. In addition, a summary of the patient insights was shared with the group. Given the physicians' collective experience with clinical trials using genomic testing and treatments, they were hopeful but pragmatic about the current application and outcomes in breast cancer. The three key take-aways from this conversation included:

1. **Patient communication and setting expectations**
   The physician group roundtable highlighted precision oncology as an important piece of the treatment puzzle. The group anticipates ongoing developments with genomically guided treatment but did convey that to date breast cancer has not experienced the same radical advancements seen in other cancers like non-small cell lung cancer. Increasingly they are being asked by patients for comprehensive genomic profiling and they spoke about the importance of managing expectations. Patients need to be aware that precision matched treatments may not always be superior to other approaches.

> *"To do a test where it's not going to yield useful information for the patient can be confusing and costly."*

2. **Testing for the right patient – the importance of utility and access**
   The physician group was experienced with genomic profiling and felt that for now it should be done in a focused manner in scenarios where it has the potential to inform an actionable outcome and/or advance research and disease understanding. Group members are often asked for their counsel by patients exploring out-of-pocket genomic profiling with private labs. While sensitive to the fact that patients place great hope in these testing opportunities, the physicians feel it is important to manage expectations. This includes assessing the likelihood that a mutation will be identified and could inform their current prognosis or enable access to targeted therapies. To date studies of patients with breast cancer have shown actionable information that influences treatment is not commonly identified. Nevertheless, they are optimistic that the number of actionable targets will increase, and the system needs to be ready.

   Continued access to clinical trials remains an important factor in advancing the science for Canadian patients. Currently there is a pan-Canadian basket trial to assess the impact of targeted agents in patients who have undergone tumor profiling and have 'druggable' changes identified in their cancers.[viii] Even

though universal genomic testing is not the standard for breast cancer, proactively communicating with patients on when and why it might or might not be useful is important in building trust. A significant challenge is the lack of consensus and direction to guide testing across the country. Even within the group different approaches were being used. Given the momentum of change in this area, the group expressed an urgent need to create a pan-Canadian process to inform appropriate molecular testing and genomic profiling in solid tumors. They also commented on the volume of tests being outsourced to private international companies, which the group felt was not only a missed opportunity for Canada, but in some instances these companies, including unregulated private companies, are preying on vulnerable patients.

The timing of genomic testing may vary with the patient and with the subtype of the tumour. If the patient has a high-risk cancer that may benefit from targeted therapy in the early setting such as treatments for BRCA mutations, genomic assessment may be crucial in that setting. If the patient has recurrent first line endocrine sensitive cancer, treatment with a CDK4/6 inhibitor and endocrine therapy is associated with a survival benefit so genomic testing may not be immediately necessary but may help determine subsequent therapies. Genomic assessment of HER2 positive cancers thus far may not be of benefit unless the tumour is resistant to treatment. Therefore, until genomic assessment is both cost effective and associated with modifications to therapy, most breast cancers should be considered for genomic assessments based on the subtype, the line of therapy and the appropriateness of treatment for the individual patient. This does not change the need for the timely approval of new therapies.

3. Thinking ahead – speed to access

As more actionable biomarkers and matched therapies are identified and proven effective, not only will the testing protocol need to evolve, so will access to those treatments. With the changes in the types of available clinical data (i.e., basket trials, umbrella trials, phase II), the group suggested creating a streamlined policy framework that enables reappraisal of the evidence. Similar to the discussion in the patient roundtable, the group urged for the implementation of a more streamlined approach between therapy approval and provincial funding decisions. One suggestion was to consider using performance standards to enable a more flexible, proactive approval process that allows for nimbler access to both therapies and testing. This could include leveraging international cooperation by setting targets for the percentage of new drugs that go through Project Orbis[ix] (an initiative led by the FDA Oncology Center of Excellence whose aim is to accelerate access to promising cancer treatments across the globe via partnership with international regulatory agencies, including Health Canada, to review drug submissions) or committing

to timelines from an FDA approval to a pCODR decision in Canada.

> *"We have to think about how Health Canada can be more creative and approachable when the magnitude of benefit is high, but the likelihood of Phase III data is low."*

Managing expectations was a prevalent theme in the discussion with physicians. They identified the importance of balancing a patient's hope with evidence-based decisions and the value of explaining why they do or do not recommend genomic testing. Although there have been marked advances already made in other cancers, the physicians have had to manage their own expectation as they await similar breakthroughs in breast cancer. Finally, they discussed how genomically driven healthcare is challenging many components of the current healthcare system. They all agreed there is a need to adjust approval and funding processes, including addressing test reimbursement, so that it can appropriately maximize the potential of this new approach.

WHERE TO NEXT? RECOMMENDATIONS FOR THE INTEGRATION OF PRECISION ONCOLOGY IN CANADA

The promise of precision oncology offers new hope to those living with breast cancer, but these advances expose gaps in our current approval and funding systems. As a patient focused organization, the CBCN sought to capture the hopes, fears, and insights of breast cancer patients and physicians to help the Canadian healthcare system successfully integrate genomically guided oncology across the country. Based on some of the gaps and needs identified in both the clinician and patient sessions, the CBCN has the following recommendations.

RECOMMENDATION #1: National Testing Framework

Both groups called for urgent action to ensure equitable access to appropriate genomic testing and treatments for all patients and their physicians, no matter where they live in Canada. This includes testing for the purposes of clinical research. Both groups saw the creation of a coordinated national approach to testing as an immediate opportunity.

The CBCN recommends the federal government along with the provinces/territories consider a national framework to guide and support a

stepwise approach to genomic testing for cancer patients and the reimbursement of these tests.

How this could work:

> Precision Oncology Task Force – The federal government and the provinces/territories to establish a Pan-Canadian expert committee to review and recommend a funded genomic testing framework for all provinces and territories. These committees should include patient and clinician representation.

RECOMMENDATION #2: Accelerated Reviews

Both groups also identified a need to adapt the current approval and funding process for innovative therapies that demonstrate a large potential magnitude of benefit. By embracing more flexible processes a responsive system can be built to fund and monitor promising therapies where ambiguity remains.

Building on the momentum of COVID-19 vaccine and testing approvals, the CBCN recommends that Health Canada and HTAs (i.e., CADTH and INESSS) develop pathways for accelerated positive recommendations based on global RWE data collection. This also includes international cooperation and more acceptance of appropriately designed phase II data and basket trials when phase III RCT trials are not feasible.

How this could work:

- Health Canada to establish dynamic and appropriate performance measures to expedite access to precision therapies for cancer. This could include leveraging international cooperation via Project Orbis to facilitate faster access and/or committing to timelines from an FDA approval to a pCODR decision in Canada.
- HTAs to create a flexible funding process that offers conditional reimbursement for NOCc therapies, even when Phase III data isn't forthcoming.

RECOMMENDATION #3: Educational Resources

Recognizing that precision oncology is not the right tool in every instance, for every patient, both groups acknowledged the importance of transparent communication on its use. The additional support of patient resources was considered a critical need to support this education and instill patient confidence and partnership.

It will be incumbent upon patient groups, cancer care agencies and health care professionals to ensure patients receive educational materials about precision oncology testing and treatment. These resources need to consider providing context and information without elevating patient anxiety. The CBCN also suggests additional information be created and made available to patients through online content – ideally in both written and video formats.

How this could work:

Patient Materials – Develop online and print resources based on patient's cancer type where physicians can direct patients for supplementary information.

Patient Navigators– Offer navigators at local cancer centres training on precision oncology so they can also be a resource for patients (consider virtual).

CONCLUSION & ACKNOWLEDGMENTS

The recommendations outlined above support the CBCN's commitment to education, advocacy and promotion of education sharing to help ensure the safety and comfort of Canadian breast cancer patients as they navigate the treatment of their disease in an evolving environment.

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APPENDIX A: KEY TERMS

Basket Trials: A type of clinical trial that tests how well a new drug or other substance works in patients who have different types of cancer that all have the same mutation or biomarker. In basket trials, patients all receive the same treatment that targets the specific mutation or biomarker found in their cancer. Basket trials may allow new drugs to be tested and approved more quickly than traditional clinical trials. Basket trials may also be useful for studying rare cancers and cancers with rare genetic changes.

Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process, or of a condition or disease. For precision oncology, a biomarker is typically a feature identified in the cancer that is associated likelihood of response to a particular drug or therapy.

Genomic Profiling: A laboratory method that is used to characterize the genetic information in a person or specific cells, as in the case of a tumor. Genomic profiling may be used to find out why some people get certain diseases while others do not, or why people react in different ways to the same drug. Knowledge of associations between genomic characteristics and drug response underlie precision medicine, where genomic profiling can be used to identify individuals more or less likely to benefit from a given drug. It may also be called: ***biomarker testing, tumor genetic testing, molecular testing, or molecular profiling***.

Precision medicine/oncology: A form of medicine that uses information about a person's or their tumor's genetic or molecular profile to prevent, diagnose, or treat disease. Sometimes referred to as ***personalized medicine***.

Real world evidence (RWE): In medicine, RWE refers to evidence obtained from outside the context of randomized controlled trials. In the case of precision breast cancer medicine, randomized controlled trials can be difficult to conduct due to the relatively small pool of patients whose molecular tests results make them candidates for a specific targeted therapy.

Targeted therapy: A type of treatment that uses drugs or other substances to identify and attack specific types of cancer cells with less harm to normal cells. Some targeted therapies block the action of certain enzymes, proteins, or other molecules involved in the growth and spread of cancer cells. Other types of targeted therapies help the immune system kill cancer cells or deliver toxic substances directly to cancer cells and kill them. Targeted therapy may or may not have fewer side effects than other types of cancer treatment. Most targeted therapies are either small molecule drugs or monoclonal antibodies.

Tumor-agnostic therapy: A type of targeted therapy that uses drugs or other substances to treat cancer based on the cancer's genetic and molecular features without regard to the cancer type or where the cancer started in the body. Tumor-agnostic therapy uses the same drug to treat all cancer types that have the genetic mutation (change) or biomarker that is targeted by the drug. Also called ***tissue-agnostic therapy***.

Notice of Compliance with conditions (NOC/c): Health Canada's authorization to market a drug with the condition that the manufacturer undertake additional studies to verify the clinical benefit. The safety of the drug must still be reasonably established.

pCODR: The role of the pan-Canadian Oncology Drug Review (pCODR) Expert Review Committee (pERC) is to assess the clinical evidence and cost-effectiveness of cancer drugs in order to make recommendations to the provinces and territories to help guide their drug funding decisions. A submission for the assessment of a cancer drug may be made by a pharmaceutical manufacturer and/or a provincially recognized clinician-based tumour group from the provinces or territories. All pERC members have experience with, and a good understanding of issues related to cancer diagnosis, treatment, and care.

APPENDIX B

The following chart outlines new targeted medications in breast cancer and their status in Canada.

Product name and active substance	Indication	Status
VITRAKVI® (larotrectinib)	Indicated for the treatment of adult and pediatric patients with solid tumours that: • Have a Neurotrophic Tyrosine Receptor Kinase (NTRK) gene fusion without a known acquired resistance mutation, • Are metastatic or where surgical resection is likely to result in severe morbidity; and • Have no satisfactory treatment options	Health Canada issued a Notice of Compliance with Conditions (NOC/c) in July 2019 CADTH recommends that Vitrakvi be reimbursed by public drug plans for treating adult and pediatric patients with locally advanced or metastatic solid tumours who have a neurotrophictyrosine receptor kinase (NTRK) gene fusion without a known acquired resistance mutation, or where surgical resection is likely to result in severe morbidity and have no satisfactory treatment options, but only if certain conditions are met.
PIQRAY® (alpelisib)	Indicated in combination with fulvestrant for the treatment of postmenopausal women, and men, with: • Hormone receptor-positive, HER2-negative • PIK3CA mutated advanced or metastatic breast cancer after disease progression following an endocrine-based regimen	Health Canada approved in August 2020 Under review with pCODR

KEYTRUDA® (pembrolizumab)	Indicated in the US for use in a variety of cancers including: • Tumor Mutational Burden-High (TMB-H) Cancer for the treatment of adult and pediatric patients with unresectable or metastatic tumor mutational burden-high Reference ID: 4766009 (TMB-H) [≥10 mutations/megabase (mut/Mb)] solid tumors, as determined by an FDA-approved test, that have progressed following prior treatment and who have no satisfactory alternative treatment options • Triple-Negative Breast Cancer (TNBC) in combination with chemotherapy, for the treatment of patients with locally recurrent unresectable or metastatic TNBC whose tumors express PD-L1 [Combined Positive Score (CPS) ≥10] as determined by an FDA approved test.2 (1.19, 2.1) Adult Indication	FDA granted approval in 2020 Health Canada NOC for other cancers but not breast cancer
ENHERTU® (trastuzumab deruxtecan)	ENHERTU (trastuzumab deruxtecan) as monotherapy is indicated for: • The treatment of adult patients with unresectable or metastatic HER2-positive breast cancer who have received prior treatment with trastuzumab emtansine (T-DM1) • The indication is authorized based on tumour response rate and durability of response. An improvement in survival has not been established.	Health Canada NOC/C

TRODELVY® (sacituzumab govitecan-hziy)	An anticipated Health Canada NOC for the indication: • For the treatment of “adult patients with unresectable locally advanced or metastatic triple-negative breast cancer (mTNBC) who have received at least two prior therapies, including at least one prior therapy for locally advanced or metastatic disease”	FDA granted approval in 2021. Currently being reviewed by Health Canada

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