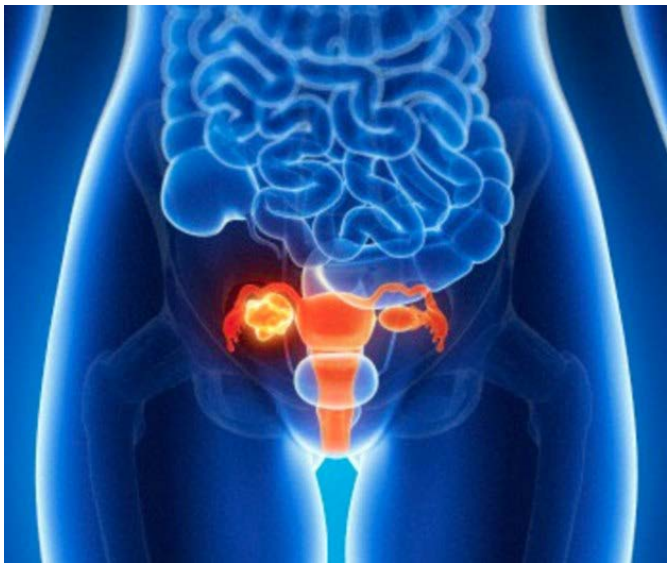
THE SOCIETY OF GYNECOLOGIC ONCOLOGY OF CANADA
LA SOCIÉTÉ DE GYNÉCO-ONCOLOGIE DU CANADA

BRCA TToT COLLABORATION

OPTIMIZING BRCA GENE TESTING FOR OVARIAN CANCER



Outcomes of a stakeholder meeting

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PREAMBLE

The recognition that BRCA and related genes play an important role in defining a distinct natural history continuum from predisposition to disease (cancer) to response to treatment requires a rethink in how we approach the treatment and care delivery for ovarian cancer, and the reduction of its burden on women. Hence the management continuum needs to be updated to reflect these unique opportunities for prevention across relatives, novel therapeutic interventions and care algorithms. The defining step in this is optimizing the identification of current patients who may benefit from contemporary treatments and families who are genetically at risk who can benefit from prevention strategies.

BRCA TtoT (Testing to Treatment) is GOC's phased strategic approach to galvanizing the wider community of stakeholders around a unifying plan to redefine the opportunities to optimize testing capacity, prevention and access to novel treatments. This initiative is designed to address the key influencers of change i.e. full stakeholder engagement, policy reform, education dissemination, and advocacy within four key pillars of focus: BRCA testing, genetic counselling, prevention and treatment.

The goal of this initial phase of the pan-Canadian BRCA initiative is to ensure that:

1. BRCA testing is routinely performed in all women with high-grade pelvic epithelial malignancy (otherwise known as epithelial ovarian carcinoma, fallopian tube carcinoma and primary peritoneal carcinoma);
2. Germline mutation testing is considered as a screening tool for patient's families as part of a prevention strategy.

BRCA TtoT is a multi-phased strategy to leverage the unique natural history continuum of BRCA and related BRCA genes in women with ovarian cancer in order to improve clinical outcomes and reduce the burden of disease on women and their families. It includes unique opportunities for improved testing capacity, prevention across relatives, novel therapeutic interventions and care algorithms. – Michael Fung-Kee-Fung, Chief Strategy Officer

INTRODUCTION

On September 9 and 10, 2016, The Society of Gynecologic Oncology of Canada (GOC) convened a stakeholder summit to discuss a pan-Canadian strategy for *BRCA* gene testing in ovarian cancer. Stakeholders [see Appendix] representing a diversity of interests, including oncologists, geneticists, genetic counsellors, patient advocates and pathologists, gathered together to:

- Create a consortium to guide clinical *BRCA* issues in ovarian cancer*****
- Establish aligned goals of the stakeholders for *BRCA* germline and tumour testing
- Define a working roadmap for implementation of *BRCA* testing
- Socialize stakeholder groups to promote ongoing collaboration

**** Note: The term "ovarian" cancer, as used in this paper, refers to a family of cancers that originate in the ovary, the fallopian tube and/or the peritoneum.***

As an outcome of the meeting, this document reviews gaps and needs in current *BRCA* testing, offers recommendations for a pan-Canadian strategy, and proposes a roadmap to deploy the proposed strategy.

No Woman Left Behind

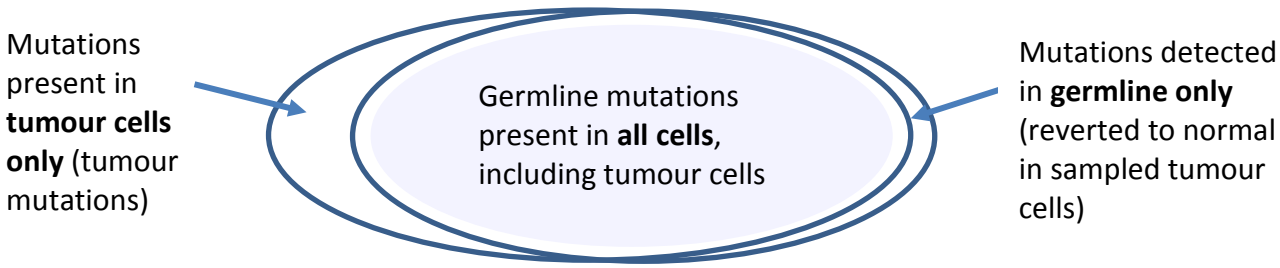
The stakeholder meeting grew out of the GOC's No Woman Left Behind campaign, which aims to improve access to *BRCA* testing for women with ovarian cancer. "When patients learn they are eligible for the test, 90% of them want it," says Dr. Paul Hoskins, GOC Past-President and a medical oncologist at the British Columbia Cancer Agency in Vancouver.

CONTEXT

The *BRCA1* and *BRCA2* genes produce proteins that help cells repair damaged DNA. Mutations in these genes result in an increased life-time risk of breast and ovarian cancer. Ten to 15% of ovarian cancers occur in women with *BRCA* mutations,[1] and 15 to 65% of women with a *BRCA* mutation will get ovarian cancer.[2] While women with *BRCA*-associated ovarian cancers tend to respond well to chemotherapy, many of them ultimately develop recurrent disease that resists treatment.

Identification of *BRCA* mutations – both in the germline and in the tumour – has become more important than ever with the advent of new drugs called Poly (ADP-ribose) polymerase (PARP) inhibitors, which stall the growth of *BRCA*-mutated tumour cells. Women with high-grade serous ovarian cancer who harbour *BRCA* mutations are candidates for these drugs.

BRCA mutations can be inherited (germline mutations) or they can arise within a tumour (tumour mutations). Furthermore, inherited *BRCA* mutations can occasionally revert to the normal *BRCA* sequence within the tumour. Such reversions, which are uncommon, typically occur in tumour cells exposed to chemotherapy. If a reversion happens early in a tumour's growth, many of the tumour cells will have the normal gene.



Germline testing (a blood test) can identify inherited *BRCA* mutations. A mutation-positive result gives patients an opportunity to use targeted chemotherapy agents, such as PARP inhibitors. Carrying a germline mutation also gives family members the opportunity to get tested themselves. If the result is positive, they can then take steps to reduce their own risk of ovarian cancer, such as prophylactic surgery.

Tumour DNA testing has recently become available in selected laboratories in Canada. This testing makes targeted treatments available to an additional group of women: those who do not carry a germline mutation, but do carry a *BRCA* mutation in their tumour. Also, by comparing results from tumour and germline tests, scientists can identify *BRCA* mutations that exist only in the tumour, referred to as somatic mutations, and thus do not "run in the family."

References

1. Norquist et al. J Clin Oncol 29:3008-3015.
2. Canadian Cancer Society, BRCA gene mutations. Accessed November 11, 2016 at: http://www.cancer.ca/en/cancer-information/cancer-101/what-is-cancer/genes-and-cancer/brca-gene-mutations/?region=on

THE CASE FOR CHANGE

Currently, women with ovarian cancer must go through several steps to obtain meaningful genetic information:

- Referral for preliminary genetic counselling and genetic testing
- Test to extract and analyze DNA
- Genetic counselling based on test results

Inequalities in awareness (among both patients and clinicians) and access to genetic services exist throughout the country, which has resulted in low referral rates and long delays. Currently, only about 20% of women with ovarian cancer are referred to genetic services. In theory, women from all over the country can have their samples shipped to the laboratories that execute tumour DNA testing, but the infrastructure to enable widespread access to this new test is not yet in place.

Missed opportunities to identify *BRCA* mutations deprive ovarian cancer patients of vital information that could affect their treatment decisions. The lack of information also deprives family members of the opportunity to get tested. This means many of them will develop ovarian and/or breast cancers that could otherwise have been prevented. Human

suffering aside, these cancers place a large burden on the health care system: based on known parameters, GOC has estimated that preventing, rather than treating, these cancers could save the health care system about $10 million per year.

The counselling link

A crucial adjunct to the testing process, genetic counselling, promotes informed choices. Pre-test counselling can help women decide whether to proceed with genetic testing. Post-test counselling can help patients interpret test results (for example, some genetic changes may have a negligible or uncertain clinical significance).

While referral rates for pre-test genetic counselling are on the rise, there is much room for improvement. Women with equivocal presentations (e.g. mucinous cancer, which doesn't ordinarily call for testing, combined with a strong family history) may get overlooked and thus miss the chance to make decisions about testing.

Paradigm shift

The recent discovery of PARP inhibitors, which achieve superior results in women with *BRCA*-associated ovarian cancer, calls for a paradigm shift in the patient testing process. GOC and associated stakeholders (including geneticists, genetic counsellors, pathologists and patient advocates), agree on the following high-level objectives:

- Germline *BRCA* testing should be routinely offered to all women with high-grade non-mucinous ovarian cancer within 3 months of diagnosis
- Pre-test genetic counselling should be made available to women eligible for germline *BRCA* testing
- Germline mutation testing should be used appropriately as a family screening and risk reduction tool
- Tumour testing should be integrated into the genetic testing pathway
- Integrated germline/tumour *BRCA* testing guidelines should be developed
- Barriers to genetic counselling should be addressed to reduce testing delays
- Uptake of opportunistic salpingectomy should reach appropriate levels. (Recent evidence indicates that most high-grade serous ovarian cancers originate in the fallopian tube.)

A rationale for *BRCA* tumour testing

- A positive result can inform decisions about targeted treatments such as PARP inhibitors
- A positive result can trigger opportunistic germline testing to determine if the mutation is present in the germline (and may also be present in family members, who then have the opportunity to consider cancer risk reduction options).
- A negative result strongly suggests (while not guaranteeing) an absence of inherited BRCA mutations, thus providing a measure of reassurance to patients and relatives.

INTEGRATED CARE MAP

"It is only through a pan-Canadian strategy that we can address the system-wide barriers to optimal care," says GOC President Dr. Walter Gotlieb, head of the Hereditary Ovarian Cancer Unit at the Jewish General Hospital in Montreal. Stakeholders agree on several key aspects of an integrated care map, as outlined below.

Enhancing existing processes

In the current models, germline testing has a low uptake, resulting in missed opportunities for risk reduction in family members. Exploring innovative models at local and regional centres can help optimize the efficiency and uptake of existing testing opportunities.

Patients in more remote areas may lack the educational and referral opportunities available to women treated at regional gynecologic oncology centres. At the same time, genetic counsellors are already strained by their current workload. There is a need for patient educational materials (e.g. brochures, videos) and for collaborative models in which genetic counsellors work with physicians to optimize patients' use of genetic services.

A few pilot projects have explored new counselling-consent-testing models, with promising results to date. Learnings from these projects can inform the development of a nationwide framework.

Integration of tumour and germline testing

Tumour testing is a vital technology. The information it provides enables women to make informed treatment decisions and allows family members take steps to reduce their own risk of ovarian cancer. GOC and associated stakeholders agree on a sequential model in which:

- Women with high-grade ovarian cancers (and other pelvic epithelial malignancies) are reflexively offered tumour testing at diagnosis via standard pathology review.
- Based on tumour test results and other factors (e.g. family history), women can elect to proceed to germline testing.

The best terms

Currently, the terms "somatic mutations" and "somatic testing" are commonly used in reference to tumour DNA. Stakeholders at the meeting propose adopting the terms "tumour mutations" and "tumour testing," especially in communications with patients, because tumour mutations can include germline and somatic mutations.

Tumour testing pathway

In view of optimizing and equalizing access to tumour testing, stakeholders propose:

- A time target of three (3) months from diagnosis to testing
- Possible reflex tumor testing in pathology laboratories

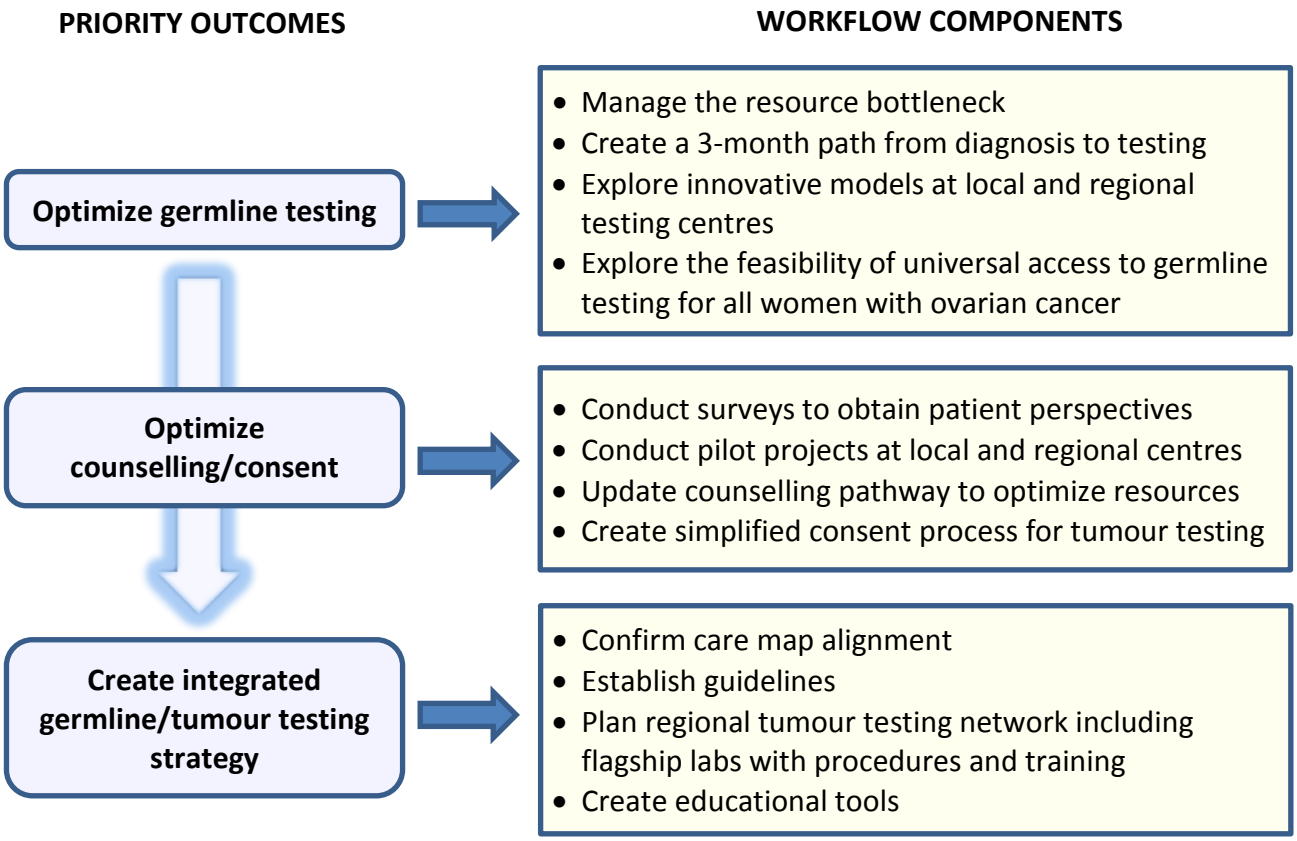
- A centralized lab testing model: rather than having many laboratories perform the test at low volume – and thus fail to gain expertise and quality assurance in a clinically meaningful timeframe – a few facilities can serve as high-volume "centres of excellence"

Consent process

Patients must provide formal consent for germline *BRCA* testing. The consent process ensures that patients understand the potential implications of testing, both for themselves and their family members. Because the test provides information about unchangeable genetic characteristics that are partly shared with relatives, knowledge of the results can have wide-ranging ramifications that extend beyond medical decision-making. For example, there is currently no provincial legislation limiting the third-party use of genetic test results, leaving individuals vulnerable to discrimination.

Tumour testing does not have the same ramifications because it does not provide conclusive information about inherited DNA and thus does not implicate relatives.

PROPOSED ROADMAP



OUTSTANDING ISSUES

To ensure the integrated care map offers a high standard of care and makes optimal use of health resources, stakeholders need to reach alignment on several outstanding questions:

Tumour/germline overlap

If tumour testing does not reveal any *BRCA* mutations, how confidently can we assume the germline is also free of such mutations? A retrospective study comparing tumour and germline DNA results in 100+ patients can help establish the concordance between these two DNA sets.

Tumour testing protocol

Tumour mutations are only present in a portion of the tumour's cells (i.e. the daughter cells of the cell in which the mutation originated). Thus, testing a single sample of a tumour may fail to identify these mutations. The optimal number of samples to test and the best way to prepare samples for testing (fresh/frozen vs soaked in paraffin embedded) have yet to be established.

Tumours can be tested not only for *BRCA* genes, but for a larger group of genes associated with an increased risk of ovarian cancer (called panel testing). This raises several questions:

- What is a reasonable number of genes to test (taking time and cost into account)?
- Which genes are most important to test?
- Should all women be tested for the same panel?

With continuous advances in knowledge and technology, these questions may need to be revisited every year or two.

Counselling protocol

The integrated care map will need to:

- Specify the mechanisms used to inform patients about their *BRCA* testing options
- Define a clear patient care trajectory for the genetic testing process
- Determine the optimal points of contact between patients and genetic service providers throughout the process
- Provide guidance on optimal delivery of genetic counselling formats

Consent protocol

Issues to resolve include:

- Who initiates the patient consent process
- When patients provide consent: in advance of, immediately before, or after surgery to remove the tumour
- Defining and developing an opt-out process that respects individual choice with regards to tumour and germline testing

Data sharing

While sharing data has potential clinical value, creating a database can be costly and logistically cumbersome. A working group can help assess the benefits and best ways of collecting, storing, and analyzing tumour test data.

Financial concerns

Funding for genetic testing and counselling services varies widely across jurisdictions. Mechanisms to equalize funding and uptake of these services need to be explored. Health-economic analyses evaluating the cost implications of different uptake scenarios – including the cost savings from risk reduction – can help drive Canada-wide testing policies.

Collaboration

The BRCA Testing to Treatment (BRCA TToT) Collaborators and Consortium will include the Canadian Association of Genetic Counsellors (CAGC), the Canadian Association of Pathologists (CAP), the Canadian College of Medical Geneticists (CCMG), Ovarian Cancer Canada (OCC) and The Society of Gynecologic Oncology of Canada (GOC).

RECOMMENDATION SNAPSHOT

- Pan-Canadian strategy for tumour/germline *BRCA* testing and genetic counselling in women with ovarian cancer
- Concurrent strategy for educating government and funders
- Sequential pathway, with tumour testing offered reflexively and germline testing offered on the basis of tumour test results and other factors
- Pathologist-initiated referrals for tumour testing
- Centralized tumour testing centres (“centres of excellence”)
- Time benchmarks for testing and counselling
- Simplified consent procedure for tumour testing
- Regular reviews of optimal gene panel to test in tumours
- Study to establish overlap between germline and tumour DNA (i.e. retrospective review of 100 patient samples)
- Health-economic analysis to establish cost implications of different uptake levels

APPENDIX: List of Stakeholders

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