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Why is tumour testing in ovarian cancer needed in Canada?

*An opinion statement developed by the National BRCA Collaborative*

**About the National BRCA Collaborative**
The National BRCA Collaborative represents an attempt to coordinate and harmonize efforts across a variety of health professionals and patient organizations whose interest lie in the diagnosis, treatment and prevention of BRCA-related malignancies. The collaboration involves the following organizations: the Canadian Association of Genetic Counselors (CAGC), the Canadian Association of Nurses in Oncology (CANO), 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).

The primary driver for BRCA TroT (Testing to Treatment) and the National BRCA Collaborative has been the lack of coordinated educational, scientific and policy approaches across the country to address the issues of unmet patient and family medical needs. In addition, although health care delivery is provincial, the benefit of a coordinated voice of patient and medical initiatives is essential to advancing BRCA initiatives by addressing the issue of disparity of knowledge, technology and practice nationwide.

**Opinion**
Tumour testing in ovarian cancer is currently needed in Canada to identify hundreds of women annually who have a BRCA mutation in their tumour tissue and thus be eligible for a PARP inhibitor. Their survival could be prolonged with personalized cancer treatment. Tumour testing can also improve the efficiency of the genetic referral process for these women, which could result in more opportunities for life-saving cancer prevention strategies among their unaffected family members.

**Background**
This year in Canada, an estimated 2,800 women will be diagnosed with ovarian cancer, and 1,800 will die within 5 years.

The majority of these women have invasive non-mucinous epithelial ovarian cancer, which includes high-grade serous carcinoma (HGSC, the most common), clear cell and endometrioid subtypes. Approximately 15-20% of women with these subtypes of ovarian cancer harbour a germline BRCA1 or BRCA2 (herein BRCA) mutation, irrespective of ethnicity or family history. Identification of BRCA mutations among women with ovarian cancer is critical because: (1) their first-degree relatives (children, siblings) have a 50% chance of carrying the same BRCA mutation, and may benefit from life-saving interventions such as bilateral salpingo-oophorectomy and mastectomy to reduce cancer risks; and (2) they may benefit from
treatment with PARP inhibitor therapy, which has been shown to prolong progression free survival\textsuperscript{5,6}.

**Problem**
Currently, all women in Canada with HGSC are eligible for publicly funded genetic counselling and genetic testing for germline \textit{BRCA} mutations. The challenge is that up to 90\% of these women do not undergo genetic testing\textsuperscript{7-10}. They are more likely to decline testing if they are older and unaware of their family history of cancer\textsuperscript{11,12}. Furthermore, not all ovarian cancer patients who are eligible for genetic testing are referred by their health care provider, resulting in lost opportunities to identify those eligible for PARP inhibitor therapy and to identify unaffected \textit{BRCA} mutation carriers among family members who can benefit from cancer screening and prevention strategies.

**Evolution of BRCA Testing**
Tumour testing represents a strategy to improve identification of patients with \textit{BRCA} mutations. Approximately 25\% of HGSC patients will have \textit{BRCA} mutations in their tumour detected by DNA sequencing. Among these, about 70\% are germline (inherited), while the remaining 30\% are somatic (acquired)\textsuperscript{13-16}. Irrespective of the type of mutation (germline or somatic), those with a \textit{BRCA} mutation identified by tumour testing are eligible for PARP inhibitor therapy, such as olaparib. Prior to 2018, Study 19 and SOLO-2 demonstrated that olaparib when used as maintenance therapy after 2\textsuperscript{nd} line chemotherapy in platinum-sensitive patients\textsuperscript{5,6} could prolong progression-free survival in \textit{BRCA} mutation carriers. In addition, in October 2018, SOLO1 demonstrated that olaparib as maintenance therapy after completion of 1\textsuperscript{st} line chemotherapy in advanced stage ovarian cancer could prolong progression-free survival in \textit{BRCA} mutation carriers by approximately \textbf{3 years} compared to placebo (standard of care)\textsuperscript{17}.

In the absence of tumour testing, only those with germline \textit{BRCA} mutations would be eligible for treatment with olaparib. Even if all women with HGSC were referred for germline genetic testing, the number of women with confirmed germline mutations would be lower than the number of women who would receive abnormal tumour test results as somatic mutations would not be detected. In addition, the implementation of a reflex tumour testing process upon a pathology diagnosis of HGSC could vastly improve the number of women tested. Therefore, the primary benefit of tumour testing is to improve identification of women eligible for olaparib therapy.

The second potential benefit of tumour testing is to triage patients for confirmatory germline genetic testing. Although all women with HGSC are eligible for genetic testing (irrespective of family history or ethnicity), only 15-20\% will have a germline \textit{BRCA} mutation. Currently, costs are incurred to the health care system (genetic counselling and testing) for all women with HGSC, including 80\% of whom are referred for genetic testing but do not carry a mutation. Given the current shortage of genetic counsellors and clinical geneticists across Canada and the prolonged wait times for consultation, there is a need to improve the efficiency of the genetic
testing process. Experience with tumour testing is evolving, however, it is foreseeable in the future that tumour testing could identify a subgroup of women with HGSC who are most likely to benefit from genetic counselling and testing. If the sensitivity and specificity of tumour testing are proven to be high, then those with \textit{BRCA} mutations detected in the tumour should be referred for genetic testing (to confirm a germline mutation), while those without \textit{BRCA} mutations might not need to be referred (unless there is a significant family history of cancer, or if other moderately penetrant gene mutations are detected in the tumour).

\textbf{Call for Action}
In summary, tumour testing in HGSC in Canada is urgently needed to identify \textit{BRCA} mutation carriers, and as soon as possible in the treatment pathway. It is estimated that 25\% of HGSC patients will have a \textit{BRCA} mutation identified in their tumour. There is now compelling evidence that these women will benefit from treatment with olaparib as maintenance therapy after completion of first-line chemotherapy. A 3-year prolongation in progression-free survival compared to conventional care is unprecedented in advanced high grade ovarian cancer.

Reflex tumour testing of all HGSC at initial diagnosis will be advantageous for these reasons:
\begin{enumerate}
\item identifies more \textit{BRCA} mutations than germline testing alone, because a subset of ovarian cancer patients will have a somatic mutation that would be missed with germline testing;
\item reduces the time to \textit{BRCA} results which are critical for treatment decisions, as reflexive tumour testing results are expected in 3-4 weeks, whereas genetic counselling and germline testing can take 3-4 months, or even longer;
\item yields a higher number of patients tested by eliminating current barriers to genetic testing, particularly with a pathology reflex test process, translating into a higher number of \textit{BRCA} mutation carriers identified and treated with therapy that could dramatically improve their survival.
\end{enumerate}

Based on the available evidence to date, the National BRCA Collaborative and GOC believe that tumour testing in ovarian cancer is needed in Canada to identify more \textit{BRCA} mutation carriers, while reducing the wait time for results to facilitate treatment decisions, and improving the efficiency of the genetic testing process.

\textbf{REFERENCES}


MISSION
The Society of Gynecologic Oncology of Canada is a non-profit organization consisting of physicians, nurses, scientists and other health care professionals specializing in gynecologic oncology. Its purpose is to improve the care of women with or at risk of gynecologic cancer by raising standards of practice, encouraging ongoing research, promoting innovation in prevention, care and discovery, and advancing awareness. GOC also seeks to disseminate knowledge to practitioners, patients and the general public on gynecologic cancer as well as cooperate with other organizations committed to women's health care, oncology, and related fields.