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COMMENTARY

Coming of age in Canada: a study of population-based genetic testing for breast and ovarian cancer

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The *BRCA1* and *BRCA2* genes are the two most commonly mutated in hereditary breast and ovarian cancer, and they are the canonical pair when it comes to cancer testing[1]. There are many other candidate genes, and large-panel testing is increasingly the norm even though not all practitioners are in agreement[2] that testing for 20 genes is better than testing for 2. Mutations are associated with lifetime risks of 80% for breast cancer and 15%–40% for cancer of the ovary or fallopian tube for *BRCA2* and *BRCA1* respectively[3]. *BRCA2* is the most frequently mutated gene in both prostate cancer[4,5] and pancreatic cancer[6–8], and patients with *BRCA2* mutations can benefit from novel therapies such as cis-platinum[9]. Annually, about 8500 cases of prostate cancer and 2150 cases of pancreatic cancer are diagnosed in Ontario, but very few of those patients are being tested for *BRCA2*.

Genetic screening is now mainstream as a consequence of diminished sequencing costs, increased public awareness, celebrity endorsement, and the now wide availability to women of preventive surgery through public and private health insurance. Intensified screening for mutation carriers with annual magnetic resonance imaging is advocated and is increasingly available[10]. Additionally, women with hereditary breast cancer can benefit from personalized treatment (both surgical and medical), which might include bilateral mastectomy, salpingo-oophorectomy, and tailored chemotherapy (cis-platinum or olaparib)[11].

The current model of delivering genetic testing for the *BRCA* genes in North America dates to the mid-1990s, at a time when genetic testing was expensive and the clinical benefits were largely unproven. Because of the high cost, public and private insurers were not willing to pay for testing for all comers. In the resulting model, a women is referred by her physician to a specialized cancer genetics clinic, where a formal assessment is conducted. If the risk estimate for carrying a mutation exceeds a threshold value (usually 10%), then genetic testing for the *BRCA* genes ensues. If not, then the woman is reassured and sent off with a number of recommendations based on her personal and family history of cancer. In many clinics, the volume of patient requests now exceeds the number of available appointments, and triage is conducted by mail or telephone. The genetics counsellor serves two purposes: informing women about cancer risk, management options, and the testing process; and ensuring that testing is rationed first to the women who are the most suitable candidates.

We believe that the current model is outdated, and here we propose an alternative model based on direct-to-consumer population-based testing. The reasons are these:

- First, a significant proportion of *BRCA* mutation carriers do not reach the 10% threshold; they therefore represent missed opportunities for identification[12].
- Very few patients with prostate cancer or pancreatic cancer are being tested. In addition, many individuals who do qualify for genetic testing fail to be identified and referred by their health care provider[12]. Many physicians do not take an adequate family history and might not be well-apprised of the criteria for testing or of the referral process.
- In some Canadian provinces, counselling services are not available outside of major centres, and the waiting period can be up to 1 year.
- Because women with a cancer diagnosis are more likely than women without cancer to have a mutation, most individuals with a mutation in Canada and the United States will not be eligible for testing until they have a personal cancer diagnosis.

The current approach might be cost-efficient, but it is not helpful if the purpose is to prevent cancer in high-risk women. Similarly, for affected patients, genetic testing—if offered through the genetics clinic—is usually postponed until well after diagnosis, and the results are not used to guide treatment.

There is some evidence from the United States that the proportion of women being tested is increasing, and the value of connecting testing to cancer prevention is increasingly being recognized[13]. As Mary-Claire King has said, "A women who is identified as a carrier after she develops cancer is a failure of cancer prevention"[14]. Some people have argued that too little is known about the risks of cancer in carriers identified without a family history, but emerging evidence now suggests that the risks in those non-familial carriers are significant and high, and that a lack of specific knowledge should not be an impediment to testing[15,a].

[a] Metcalfe K, Lubinski J, Gronwald J, *et al*. The risk of breast cancer in *BRCA1* and *BRCA2* mutation carriers without a first-degree relative with breast cancer. *Clin Genet* [submitted].

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We propose offering genetic testing for *BRCA1* and *BRCA2* to all women and men who wish to be tested, using an Internet-based system. Pretest genetic counselling could be Web-based. Face-to-face genetic counselling could be limited to the small percentage of women who are identified as mutation carriers.

We are not necessarily asking the government or insurance companies to pay. A test that could be done for $200 is within reach of most people. We foresee that, with this unrestricted model, a greater number of mutation carriers will be detected in the population, and a higher proportion of mutation carriers will be identified before they are diagnosed with cancer. Affected women will be able to take advantage of preventive surgeries and magnetic resonance imaging screening.

With those goals in mind, we launched the Screen Project in March 2017. In collaboration with Veritas Genetics (Boston, MA, U.S.A.), we will offer and evaluate population-based genetic testing for *BRCA* mutations across Canada. Testing—only for *BRCA1* and *BRCA2*—is offered to all Canadian women and men who are 18 years of age or older. A guided direct-to-consumer approach through the study Web site (http://www.thescreenproject.ca/) is used to enrol individuals. All individuals with a pathogenic mutation in either gene will be contacted by our team of genetic counsellors in person or by telephone to discuss their options for cancer prevention. Our team will also facilitate a referral to a local genetics clinic for long-term follow-up. The cost of this *BRCA* genetic test is US$165.

We estimated the frequency of *BRCA* mutations in the general population to be between 1 in 200 and 1 in 400. Among the first 150 people tested, we identified 5 with mutations (1 in 50); of those 5, 3 did not meet provincially based criteria for publicly funded testing.

We believe that population-based genetic testing should currently be limited to *BRCA1* and *BRCA2*, although support for including *PALB2* is growing. Most variants in *BRCA1* and *BRCA2* are readily classified as pathogenic and non-pathogenic; the intermediate-risk class is small. Much information about the associated cancer risks and the benefits of surgical intervention is available[3,11]. Women with a deleterious mutation would be at sufficiently high risk to qualify for surgical intervention depending on their age[16,17].

Through the Screen Project, we will evaluate the feasibility and also the interest and yield of genetic testing for *BRCA* mutations in Canada when offered direct-to-consumer at a minimum charge. We hope to build a cost-effective strategy for lowering the incidence of and mortality from two of the most common cancers in Canada.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

AUTHOR AFFILIATIONS

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