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REVIEW

Evolution of genetic assessment for BRCA-associated gynaecologic malignancies: a Canadian multisociety roadmap

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ABSTRACT

The landscape of genetic testing in ovarian cancer patients has changed dramatically in recent years. The therapeutic benefits of poly ADP-ribose polymerase (PARP) inhibitors in treatment of *BRCA1/2*-related ovarian cancers has resulted in an increased demand and urgency for genetic testing results, while technological developments have led to widespread use of multi-gene cancer panels and development of tumour testing protocols. Traditional genetic counselling models are no longer sustainable and must evolve to match the rapid evolution of genetic testing technologies and developments in personalized medicine. Recently, representatives from oncology, clinical genetics, molecular genetics, pathology, and patient advocacy came together to create a national multi-disciplinary Canadian consortium. By aligning stakeholder interests, the BRCA Testing to Treatment (BRCA TtoT) Community of Practice aims to develop a national strategy for tumour and germline *BRCA1/2* testing and genetic counselling in women with ovarian cancer. This article serves to provide an overview of the recent evolution of genetic assessment for *BRCA1/2*-associated gynecologic malignancies and outline a Canadian roadmap to facilitate change, improve genetic testing rates, and ultimately improve outcomes for hereditary ovarian cancer patients and their families.

the patients with cancer and affords cancer risk-reduction opportunities for their family members. For example, in *BRCA1/2* mutation carriers unaffected by ovarian cancer, a prophylactic bilateral salpingo-oophorectomy is associated with an 80% decrease in the risk of ovarian cancer, and a 77% reduction in all-cause mortality.¹³

Somatic *BRCA1/2* mutations, which are acquired and limited to the tumour tissue, similarly have therapeutic implications for patients but do not modify familial cancer risk. In the >20% of high-grade epithelial ovarian cancers associated with *BRCA1/2* mutations, approximately 75% arise as a result of inherited mutations with the remainder being the result of somatic mutations.¹⁴ This is therapeutically important as in May 2016, Health Canada approved the use of poly ADP-ribose polymerase (PARP) inhibitors for treatment of platinum-sensitive, relapsed *BRCA1/2*-mutated (germline or somatic), high-grade serous epithelial ovarian, fallopian tube or primary peritoneal cancers.¹⁵ The direct link between genetic testing and cancer treatment has led to stresses on the Canadian health-care system, including an increase in requests by medical and surgical oncologists for both tumour testing and rapid clinical genetic assessments. The traditional germline *BRCA1/2* testing paradigm (counsel then test) involves a pre-test consultation with a genetic counsellor and/or clinical geneticist

INTRODUCTION AND DRIVERS FOR CHANGE IN CANADA

Each year, 2800 Canadian women are diagnosed with ovarian cancer and 1800 die of the disease, making it the fifth leading cause of cancer deaths in Canadian women.¹ An estimated 20%–30% of epithelial ovarian cancers are related to an inherited predisposition.^{2–9} Most hereditary ovarian cancers are caused by inherited (germline) mutations in the *BRCA1* and *BRCA2* genes, which result in a 14%–44% cumulative lifetime risk¹⁰; however, the contribution of other genes is becoming increasingly apparent (table 1).^{8 9 11 12} In the context of ovarian cancer, identification of a germline *BRCA1/2* mutation has therapeutic implications for

Table 1 Germline mutations in epithelial ovarian cancer

Gene	Frequency in ovarian cancer	Lifetime risk
Hereditary breast and ovarian cancer (<i>BRCA1</i> , <i>BRCA2</i>)	15%–21% ^{8,9}	17%–44% ¹⁰
Lynch syndrome (<i>MLH1</i> , <i>MSH2</i> (<i>EPCAM</i>), <i>MSH6</i> , <i>PMS2</i>)	0.5% ^{8,9}	6%–12% ¹²
Additional genes (<i>BRIP1</i> , <i>RAD51C</i> , <i>RAD51D</i>)	2.5%–3% ^{8,9}	10%–15% ⁹



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prior to germline genetic testing. This resource-heavy paradigm is no longer sustainable with current clinical resources. Historically, tumour testing for somatic mutations did not analyse genes involved in hereditary cancer, but the addition of *BRCA1/2* to tumour testing necessitates the introduction of familial implications to the informed consent process.¹⁶ Overall, the impact of PARP inhibitors and associated demands for somatic and germline *BRCA1/2* genetic testing has opened the door to a new era in genetic care for Canadians. To fully realise the potential of genetics in the care of patients with ovarian cancer, there exists an immediate need for structural changes within the existing system, thereby allowing for the provision of comprehensive and timely care for this patient group.

Until now, Canada has lacked a national forum to articulate and address the scientific, therapeutic and operational drivers described above. To this end, the Society of Gynecologic Oncology of Canada (GOC) initiated a broad-based strategic vision: BRCA Testing to Treatment (TtoT). This vision continuum seeks the national integration and optimisation of the patient's journey with rapidly evolving scientific and therapeutic opportunities, with an initial goal of improving uptake and access to genetic testing. In 2016, the GOC Communities of Practice group launched the BRCA TtoT Community of Practice, creating a multidisciplinary, Canadian *BRCA* consortium of experts and stakeholders, including members of the GOC, the Canadian College of Medical Geneticists, the Canadian Association of Genetic Counsellors, the Canadian Association of Pathologists and patient advocates from Ovarian Cancer Canada. The mission of the BRCA TtoT Community of Practice is to review and describe a road map for this journey as a guide to support health systems in their care delivery for this population. Herein, we provide an overview of the state of somatic and germline *BRCA1/2* genetic testing and genetic counselling in Canada and outline national priorities to increase timely access for all Canadian women with a diagnosis of epithelial ovarian cancer.

CHALLENGES AND OPPORTUNITIES IN *BRCA1/2* ASSESSMENT IN CANADA

Identification of a germline gene mutation within a family provides members with opportunities for high-risk cancer screening and cancer risk reduction. In the context of ovarian cancer, due to a lack of effective screening, it is recommended that women with a known identified predisposition undergo prophylactic bilateral salpingo-oophorectomy.¹⁷ In traditional germline genetic testing models, patients with ovarian cancer are referred to clinical genetics by their surgeon and/or oncologist. Germline testing and result disclosure is then facilitated over two appointments. During a pre-test appointment, a genetic counsellor reviews the patient's personal and family history to determine the appropriate germline genetic test and provides thorough counselling regarding the potential advantages and disadvantages, as well as the limitations of testing. This allows the patient to make an informed choice about whether to have germline genetic testing. During a post-test appointment, a genetic counsellor reviews the germline genetic test result, reiterating any test limitations and implications the result may have for the patient and their family members. In addition to informing future cancer risks for patients and their family members, germline genetic testing now also has the potential to directly influence ovarian cancer treatment because of the additive value of PARP inhibitors in patients with *BRCA1/2* mutations.^{18–20}

Despite multiple guidelines recommending genetic testing for all patients with non-mucinous epithelial ovarian cancer,

irrespective of additional personal cancer history, family history or ethnicity,^{17 21 22} published studies consistently show that <25% of these women are referred for germline genetic testing using the traditional germline testing model described above.^{7 23–25} National criteria for hereditary breast and ovarian cancer genetic testing do not exist in Canada and each province follows their own formal or informal criteria (see online supplementary file 1). A recent review article by BRCA TtoT members identified process issues, geographic access and lack of physician knowledge as major barriers to genetic testing.²⁶ Current under-referral practices prevent opportunities for personalised treatment of ovarian cancer as well as cancer risk reduction in at-risk relatives. While there is an increased awareness of this gap in care, a simple solution resulting in the ideal of 100% genetic referral/testing rates remains elusive. In 2016, BRCA TtoT members conducted a survey of Canadian cancer genetics clinics and found that turnaround time for genetic test results was up to 8 months and wait-times for pre-test counselling ranged from 2 months to 2 years overall, with faster (3–5 months) pre-test wait-times for patients with ovarian cancer specifically (unpublished data). Thus, simply increasing genetics referral rates for patients with ovarian cancer will not likely result in timely access to genetic information and may serve to create longer genetics wait-times for all patients. The current wait-times in Canada for traditional germline *BRCA1/2* assessment are prohibitive for potential treatment decisions.

Since the discovery of the *BRCA1* and *BRCA2* genes in the mid-1990s,^{27 28} genetic testing technologies have evolved significantly. Previously, genetic testing relied on slow and expensive techniques. The development and widespread use of high-throughput massively parallel sequencing (also known as next-generation sequencing (NGS)) technologies has dramatically reduced the cost and turnaround time of genetic testing. Central to this discussion, genetic testing of *BRCA1/2* alone had a cost of over US\$3000 and results took months to complete. The increased sequencing capacity of NGS has also facilitated the discovery of moderately penetrant genes. The US Supreme Court's ruling that genes cannot be patented²⁹ resulted in an explosion of genetic testing companies offering hereditary breast and ovarian cancer multigene panel tests. Today, commercial companies in the USA offer multigene cancer panels for as little as US\$249, providing results in 3–4 weeks. The American shift to panel-based genetic testing for hereditary breast and ovarian cancer likely catalysed the development of similar panels in Canadian genetic testing laboratories.

Despite the obvious benefits of NGS, panel-based germline genetic testing has resulted in significant practice changes for genetic counsellors.^{30 31} Currently, many hereditary breast and ovarian cancer gene panels include moderate penetrance genes with limited information on relevant cancer risks or recommendations regarding cancer screening and risk reduction. Testing multiple genes also increases the likelihood of identifying one or more variants of uncertain significance (often referred to as VUS). Even relatively small panels return a VUS result in >20% of cases.^{32 33} Rather than counselling patients extensively about two genes, genetic counsellors must counsel patients broadly about multiple genes, focussing on the potential uncertainty associated with test results.^{30 31} While shifting practice from single gene to panel-based germline testing, genetic counsellors are also adjusting to advances in precision medicine. In the past, the primary role of genetic testing was to inform patients and their families of their future cancer risks and available options for high-risk screening and risk reduction, not to guide the treatment of a current ovarian cancer.³⁴ The new utility of genetic

testing to inform cancer treatment alters the context of pre-test counselling, moving from a shared decision-making process to a more directive discussion. The Health Canada approval of PARP inhibitors for the treatment of *BRCA1/2*-related ovarian cancers in the recurrent setting has created a sense of urgency for genetic testing, applying more pressure and increasing clinical load on already strained genetic counselling resources. Future uses of PARP inhibitors are anticipated, including 1) early maintenance therapy for ovarian cancer (frontline use) and 2) treatment in other disease sites, such as breast and prostate cancer. In fact, PARP inhibitors have already received US Food and Drug Administration approval for use in the treatment of HER2-negative metastatic breast cancer in women with germline *BRCA1/2* mutations.³⁵ Continued advances in personalised cancer treatment will further increase demands for timely genetic testing.

NGS technologies have also facilitated the expansion of testing DNA extracted from formalin-fixed, paraffin-embedded (FFPE) tumour tissues. Currently, NGS panels are used in Canada to detect somatic mutations in tumour tissue to identify therapeutic biomarker targets for personalised cancer treatments (eg, in non-small cell lung cancer, colorectal cancer and melanoma). The availability of FFPE tumour tissue NGS testing, including testing of *BRCA1/2* on ovarian tumour tissue, provides an ability to test, ascertain and treat additional women with somatic *BRCA1/2* mutations, who would otherwise be missed by the traditional germline testing models. Tumour testing has the potential to efficiently capture both germline and somatic mutations, identifying all patients who are eligible for PARP inhibitors and those at risk of a germline mutation. However, tumour genetic testing for *BRCA1/2* is not currently funded through the Canadian public healthcare system and access is limited to research initiatives, clinical trials, or private testing. Expertise in technical and interpretive aspects of NGS testing on DNA from FFPE tissue, which is the most obtainable source of tumour tissue in the current Canadian pathology context, is also still evolving in Canadian laboratories. While many Canadian laboratories already offer a variety of NGS-based tests, including germline testing (eg, hereditary breast and ovarian cancer panels) and somatic testing of FFPE tissues for biomarkers, defining optimal approaches to

laboratory testing for *BRCA1/2* testing in FFPE DNA will be an important enabler of the tumour-first approach. In addition, there is no national system to provide governance and resources to validate a tumour-first assay in all Canadian centres, and no guarantee of funding/reimbursement by the provincial Ministries of Health once such an assay is validated.

Current genetic counselling models must evolve to match the rapid evolution of genetic testing technologies, tissues tested (eg, tumour or germline) and developments in personalised medicine. Importantly, when offered genetic testing, most patients with ovarian cancer proceed with testing^{7 36–40} and would prefer to receive genetic testing early on in the course of their disease.^{36 41} In a recent prospective analysis of >10 000 individuals referred for *BRCA1/2* genetic counselling and testing, over 85% of patients with ovarian cancer consented to genetic testing and the most common reason to decline testing was concern about out-of-pocket costs, which is irrelevant in the Canadian context.⁴⁰ The potential therapeutic impact of genetic testing, the widespread use and broad scope of NGS panels, and the consistently high acceptance of genetic testing among patients with ovarian cancer, makes this population of women uniquely suited to consider alternative methods of genetic counselling.

NATIONAL PRIORITIES TO IMPROVE ASSESSMENT AND TESTING FOR ALL OVARIAN CANCERS

Several adaptations to the traditional cancer genetics model are being considered among cancer genetics clinics in Canada and elsewhere. Different models will suit different jurisdictions. Current models can be dichotomised to those where genetic testing is facilitated by genetics professionals and those where genetic testing is facilitated by the oncology team (table 2). Examples of the former include pathology-mediated genetics referrals, genetic counsellor-mediated referrals and embedding genetic counsellors in oncology clinics. Pathology-mediated referrals may include reflexive statements or opt-out genetics referrals. In British Columbia, genetic testing rates improved to 43% following the addition of a reflexive statement on the pathology report of all high-grade serous ovarian cancers

Table 2 Alternative models of genetic counselling and testing for patients with ovarian cancer

Model	Description	Impact
Opt-out genetics referral pathway	Unless their surgeon specifies otherwise, genetics referrals are processed automatically based on a list of newly diagnosed patients with ovarian cancer generated from the electronic health record.	Increases referral rates Decreases time from diagnosis to referral May result in overall increased wait-times
Genetics-mediated referrals	Genetic counsellors identify eligible patients and recommend genetics referrals. Can be done by attendance at oncology meetings or chart review.	Increases referral rates Requires added genetic counselling resources May result in overall increased wait-times
Embedding genetic counsellors into oncology clinics	Genetic counsellors are present in oncology clinics to identify eligible patients and coordinate genetic counselling during oncology visits.	Increases referral rates Coordinated counselling may reduce wait-times Requires added genetic counselling resources
Mainstreaming	Genetic testing ordered by the oncology team with support from clinical genetics.	Increases genetic testing rates Decreases wait-times Absence of extensive pre-test counselling
DNA-Direct	Genetic testing ordered remotely following genetics referral using an information sheet, pre-test video and blood collection kit.	May increase genetic testing rates Decreases wait-times Absence of extensive pre-test counselling
DNA BONus	Genetic testing ordered by the oncology team using a pre-test information sheet.	May increase genetic testing rates Decreases wait-times Absence of pre-test counselling
Reflexive tumour testing	Genetic testing is ordered reflexively on ovarian tumour tissue.	Rapid access to genetic information for treatment Minimise number of germline tests required Absence of pre-test counselling Concerns about patient consent

recommending a genetics referral.⁴² Similar processes have been adopted by other Canadian centres. One Ontario centre has adopted an opt-out genetics referral pathway, where a woman is identified through a hospital's electronic health record system as a patient who is newly diagnosed with a non-mucinous epithelial ovarian cancer by a pathology report. The genetics clinic receives a monthly list of such patients, and unless instructed otherwise by the patient's surgeon within 2 months of surgery, a referral for genetic counselling/testing is automatically processed. This model resulted in significant improvements in genetics referral rates, with 77% of patients with serous ovarian cancer referred in the first year of implementation.²⁵ In some centres, genetic counsellors help to increase genetic referral rates for patients with ovarian cancer. For example, Eichmeyer *et al* reported that a weekly review of all new oncology patients by a genetic counsellor improved cancer genetics referral rates from 50% to 70% overall, from 29% to 91% for patients with ovarian cancer and increased genetic counselling volumes by 11%.⁴³ Another study reported that genetics referral rates for patients with ovarian cancer improved from 26.7% to 51.7% after a genetic counsellor began attending oncology tumour board meetings.⁴⁴ This process has been adopted in Nova Scotia, whereby a genetic counsellor attends gynaecologic oncology tumour board meetings to identify eligible patients with ovarian cancer. Embedding genetic counsellors into gynaecologic oncology clinics is another effective way to increase genetics referral rates and improve the coordination of patient appointments. In one Australian centre, average referral rates improved from 54% to 85%, reaching 97% in the second year following implementation, and average counselling time decreased from 120 to 54 min.³⁷ A similar process at a large academic centre in the USA improved referral rates from 21% to 44% and decreased the average time from referral to genetic counselling from 2.52 to 1.67 months.⁴⁵

Many hospitals have implemented alternative models where genetic testing is not directly facilitated by genetic counsellors. For example, genetic testing may be ordered directly by oncologists and the oncology team, with support from clinical genetics. This model, often referred to as 'mainstreaming', was popularised by the Mainstreaming Cancer Genetics Programme in the UK.³⁸ In the UK, implementation of the mainstreaming model resulted in a 100% genetic testing rate for women with non-mucinous ovarian cancer, with high patient and clinician satisfaction and reduced patient wait-times.³⁸ In the Netherlands, all patients with breast cancer referred for genetic testing were given the option of counselling using a traditional or 'DNA-Direct' model, where patients were mailed an informational letter, a website link to a pre-test video and a blood collection kit.^{46 47} The majority of patients (59%) chose the DNA-Direct model, of whom 100% completed genetic testing and 89% stated they would choose the DNA-Direct model again.⁴⁶ A similar 'DNA BONUS' model in Norway offered genetic testing to all newly diagnosed patients with breast and ovarian cancer using an information sheet in lieu of pre-test genetic counselling, with 68% of patients with ovarian cancer accepting genetic testing.³⁹ Variations of these mainstreamed genetic testing models have been adopted by hospitals in several Canadian provinces and studies are ongoing to evaluate the effectiveness and acceptability of this process in Canada.

Despite their benefits, current modifications to the traditional germline genetic testing model continue to present potential barriers, especially to women living in areas distant from academic centres. Clinical genetic services are often affiliated with urban, academic centres. Telephone and telemedicine genetic counselling alternatives are available; however,

<10% of genetic counsellors routinely provide these services.⁴⁸ Geographical access is a particular concern in Canada as 14%–53% of Canadians live in rural areas.⁴⁹ Alternative models, which increase genetic testing access without also increasing the systemic burden associated with in-person appointments, are particularly useful, especially in rural catchments.

There may be no 'one-size-fits-all' solution to improve current germline genetic testing protocols. Various medical centres have different levels of human and financial resources available to support the implementation and validation of new genetic testing and/or referral practices. An American study demonstrated that even a multipronged approach, which included embedding a genetic counsellor into oncology clinics, genetics review of medical records to identify eligible patients and oncologist-ordered genetic testing, did not result in 100% genetic testing rates for patients with ovarian cancer.⁵⁰ A possible solution, as an adjunct or in replacement to the current models, is the implementation of reflexive tumour testing of all non-mucinous epithelial ovarian cancers as a strategy to eliminate potential physician, patient, geographic and system barriers.^{16 26 51} Tumour testing in ovarian cancers could serve as a molecular screening test to identify patients who 1) may benefit from PARP inhibitors and 2) require genetic counselling and/or germline genetic testing. Since a minority of ovarian cancers are related to *BRCA1/2* mutations (15%–20% germline; 5% somatic) and tumour testing has the ability to identify both germline and somatic mutations, a 'tumour first' strategy would significantly reduce the number of unnecessary genetics referrals, simplify counselling and increase the efficiency of genetics clinics.

Irrespective of the advantages of tumour-first genetic testing, there remain concerns of how informed patient consent is obtained and if widespread genetic testing could result in negative psychosocial impacts that were previously alleviated by in-depth pre-test counselling and comprehensive informed consent. Concerns about genetic discrimination have also been cited as barriers for clinician referral⁵² and patient uptake of germline testing for hereditary cancer.⁵³ As of May 2017, the Canadian Genetic Non-Discrimination Act (GNA) prohibits individuals from being required to undergo a genetic test or disclose genetic test results in order to 1) access goods or services, and 2) enter into or continue a contract or agreement.⁵⁴ Unlike its American counterpart, the Genetic Information Non-Discrimination Act of 2008, GNA does not provide protection from discrimination based on one's family medical history.^{54 55} Additional patient barriers to uptake of germline testing may exist, including concern about stigmatisation, negative psychological reaction and concerns related to reactions of family members. In considering a reflexive tumour-first genetic testing strategy, it is critical to recognise that tumour results contain both germline and somatic mutations. Identifying a hereditary cancer gene mutation in an individual's tumour tissue does not necessarily diagnose that individual with a hereditary cancer syndrome, nor does it make their family members eligible for predictive genetic testing. Thus, thorough genetic counselling would still be provided to patients and their families after positive tumour testing, yet prior to germline testing, to minimise the potential for misunderstanding and negative impacts, and promote an informed patient choice. Regardless of a patient's personal decision to proceed with germline genetic testing, treatment decisions can be made based on tumour test results alone.

Overall, the national priorities to improve assessment and treatment of women with epithelial ovarian cancer in Canada, as defined during prior meetings of the BRCA TtoT Community of Practice, are as follows:

1. Genetic testing should be routinely performed in all women with non-mucinous epithelial ovarian cancer. The time from cancer diagnosis to genetic testing results should be monitored and Canadian benchmarks should be established to define clinically appropriate wait-times.
2. A reflex, tumour-first testing model is preferred, due to its ability to detect both somatic and germline *BRCA1/2* cases, and to ensure thorough access to all patients without dependence on a referral system. Definition of laboratory best practices for tumour-first testing would be an important enabler of this approach.
3. In anticipation of a reflex tumour-based genetic testing programme, a pan-Canadian strategy should be developed to facilitate implementation of a tumour-based process for *BRCA1/2* testing.
4. Recognising the overall clinical, pathology and laboratory expertise required, Canadian centres of excellence should be established to enable more rapid access to tumour testing and development/dissemination of best practices.
5. Alternative strategies for germline genetic testing and genetic counselling are required to address barriers, recognising that a one-size-fits-all strategy may not be feasible for all clinics and patients.
6. Cascade germline genetic testing should be encouraged in relatives of mutation carriers, such that at-risk women can make an informed decision regarding risk reduction strategies (ie, prophylactic bilateral salpingo-oophorectomy).
7. Educational strategies should be developed to increase oncologist awareness and understanding of genetic testing options. Oncologists should be comfortable with facilitating testing of their patients and managing their care according to the genetic test results.
8. Development and implementation of changes should involve the continued evaluation of sustainability, acceptability among patients and clinicians, and the cost-effectiveness of this strategy in a publicly-funded healthcare system.
9. Initiate dialogue with laboratory funders (cancer agencies, provincial ministries of health) to facilitate new funding models for genetic testing in the context of incident cases of breast and ovarian cancer.

CONCLUSIONS

The landscape of genetic testing for patients with ovarian cancer has changed dramatically since the discovery of the *BRCA1/2* genes. Where previous guidelines stressed the importance of reserving genetics referrals for patients with ovarian cancer who had a relevant family history, it is now widely accepted that all women with non-mucinous epithelial ovarian cancer should be referred for genetic testing, irrespective of other factors. Where previously the cost of genetic testing required strict criteria to limit the number of tests and genes analysed, now relatively inexpensive multigene panels are widely available. Where the benefit of genetic testing stressed the notion of cancer prevention, now results have a direct impact on cancer treatment. Where patients and clinicians may have had concerns about insurability, now Canadian laws exist to protect against the inappropriate use of genetic information. In 2018, despite increased awareness and technological advances, many patients with ovarian cancer still do not have timely access to genetic information. Collaborations between oncology, genetics and others have facilitated the development of alternative models of genetic testing, including an opt-out genetics referral pathway, genetic counsellors embedded in oncology clinics

and oncologist-directed genetic testing. These modifications to traditional genetic counselling models create opportunities for timely genetic testing in patients with ovarian cancer; however, potential barriers to genetic testing remain. The BRCA TtoT national Community of Practice supports the development of a reflexive tumour testing model to provide rapid treatment-based information, overcome existing barriers, improve efficiencies of traditional genetic service delivery and allow for timely genetic counselling and testing of patients with ovarian cancer and their at-risk family members.

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