

Cancer prevention through cascade genetic testing: A review of the current practice guidelines, barriers to testing and proposed solutions

Up to 400,000 women in the United States carry a gene mutation that translates to a high risk for breast and ovarian cancer. Cascade genetic testing may prevent the development of these cancers in relatives of those with genetic mutations. The authors highlight which patient populations would benefit from such testing, as well as strategies to increase benefits for affected patients.

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IN THIS ARTICLE

CASE Woman with BRCA2 mutation

An 80-year-old woman presents for evaluation of newly diagnosed metastatic pancreatic adenocarcinoma. Her medical history is notable for breast

cancer. Genetic testing of pancreatic tumor tissue detected a pathogenic variant in *BRCA2*. Family history revealed a history of melanoma as well as bladder, prostate, breast, and colon cancer. The patient subsequently underwent germline genetic testing with an 86-gene panel and a pathogenic mutation in *BRCA2* was identified.

Watch a video of this patient and her clinician, Dr. Andrea Hagemann: <https://www.youtube.com/watch?v=TapPsJHLfX8&t=6s>.



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The authors report no financial relationships relevant to this article.

doi:10.12788/obgm.0158

Methods of genetic testing

It is estimated that 1 in 300 to 1 in 500 women in the United States carry a deleterious mutation in *BRCA1* or *BRCA2*. This equates to between 250,000 and 415,000 women who are at high risk for breast and ovarian cancer.¹ Looking at all women with cancer, 20% with ovarian,² 10% with breast,³ 2% to 3% with endometrial,⁴ and 5% with colon cancer⁵ will have a germline mutation predisposing them to cancer. Identification of germline or somatic (tumor) mutations now inform treatment for patients with cancer. An equally important goal of germline genetic testing is cancer prevention. Cancer prevention strategies include risk-based screening for breast, colon, melanoma, and pancreatic



cancer and prophylactic surgeries to reduce the risk of breast and ovarian cancer based on mutation type. Evidence-based screening guidelines by mutation type and absolute risk of associated cancers can be found on the National Comprehensive Cancer Network (NCCN).^{6,7}

Multiple strategies have been proposed to identify patients for germline genetic testing. Patients can be identified based on a detailed multigenerational family history. This strategy requires clinicians or genetic counselors to take and update family histories, to recognize when a patient requires referral for testing, and for such testing to be completed. Even then the generation of a detailed pedigree is not very sensitive or specific. Population-based screening for high-penetrance breast and ovarian cancer susceptibility genes, regardless of family history, also has been proposed.⁸ Such a strategy has become increasingly realistic with decreasing cost and increasing availability of genetic testing. However, it would require increased genetic counseling resources to feasibly and equitably reach the target population and to explain the results to those patients and their relatives.

An alternative is to test the enriched population of family members of a patient with cancer who has been found to carry a pathogenic variant in a clinically relevant cancer susceptibility gene. This type of testing is termed *cascade genetic testing*. Cascade testing in first-degree family members carries a 50% probability of detecting the same pathogenic mutation. A related testing model is *traceback testing* where genetic testing is

performed on pathology or tumor registry specimens from deceased patients with cancer.⁹ This genetic testing information is then provided to the family. Traceback models of genetic testing are an active area of research but can introduce ethical dilemmas. The more widely accepted cascade testing starts with the testing of a living patient affected with cancer. A recent article demonstrated the feasibility of a cascade testing model. Using a multiple linear regression model, the authors determined that all carriers of pathogenic mutations in 18 clinically relevant cancer susceptibility genes in the United States could be identified in 9.9 years if there was a 70% cascade testing rate of first-, second- and third-degree relatives, compared to 59.5 years with no cascade testing.¹⁰

Gaps in practice

Identification of mutation carriers, either through screening triggered by family history or through testing of patients affected with cancer, represents a gap between guidelines and clinical practice. Current NCCN guidelines outline genetic testing criteria for hereditary breast and ovarian cancer syndrome and for hereditary colorectal cancer. Despite well-established criteria, a survey in the United States revealed that only 19% of primary care providers were able to accurately assess family history for *BRCA1* and *2* testing.¹¹ Looking at patients who meet criteria for testing for Lynch syndrome, only 1 in 4 individuals have undergone genetic testing.¹² Among patients diagnosed with breast and ovarian cancer, current NCCN guidelines recommend germline genetic testing for all patients with epithelial ovarian cancer; emerging evidence suggests all patients with breast cancer should be offered germline genetic testing.^{7,13} Large population-based studies have repeatedly demonstrated that testing rates fall short of this goal, with only 10% to 30% of patients undergoing genetic testing.^{9,14}

Among families with a known hereditary mutation, rates of cascade genetic testing are also low, ranging from 17% to 50%.¹⁵⁻¹⁸ Evidence-based management guidelines, for both hereditary breast and ovarian cancer as well as Lynch syndrome, have been shown

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Only 10% to 30% of patients with breast cancer have undergone genetic testing, although emerging evidence suggests all patients should undergo this type of testing

to reduce mortality.^{19,20} Failure to identify patients who carry these genetic mutations equates to increased mortality for our patients.

Barriers to cascade genetic testing

Cascade genetic testing ideally would be performed on entire families. Actual practice is far from ideal, and barriers to cascade testing exist. Barriers encompass resistance on the part of the family and provider as well as environmental or system factors.

Family factors

Because of privacy laws, the responsibility of disclosure of genetic testing results to family members falls primarily to the patient. Proband education is critical to ensure disclosure amongst family members. Family dynamics and geographic distribution of family members can further complicate disclosure. Following disclosure, family member gender, education, and demographics as well as personal views, attitudes, and emotions affect whether a family member decides to undergo testing.²¹ Furthermore, insurance status and awareness of and access to specialty-specific care for the proband's family members may influence cascade genetic testing rates.

Provider factors

Provider factors that affect cascade genetic testing include awareness of testing guidelines, interpretation of genetic testing results, and education and knowledge of specific mutations. For instance, providers must recognize that cascade testing is not appropriate for variants of uncertain significance. This can lead to unnecessary surveillance testing and prophylactic surgeries. Providers, however, must continue to follow patients and periodically update testing results as variants may be reclassified over time. Additionally, providers must be knowledgeable about the complex and nuanced nature of the screening guidelines for each mutation. The NCCN provides detailed recommendations by mutation.⁷ Patients may benefit from care with cancer specialists who are aware of the guidelines,

particularly for moderate-penetrance genes like *BRIP1* and *PALB2*, as discussions about the timing of risk-reducing surgery are more nuanced in this population. Finally, which providers are responsible for facilitating cascade testing may be unclear; oncologists and genetic counselors not primarily treating probands' relatives may assume the proper information has been passed along to family members without a practical means to follow up, and primary care providers may assume it is being taken care of by the oncology provider.

Environmental or system factors

Accessibility of genetic counseling and testing is a common barrier to cascade testing. Family members may be geographically remote and connecting them to counseling and testing can be challenging. Working with local genetic counselors can facilitate this process. Insurance coverage of testing is a common perceived barrier; however, many testing companies now provide cascade testing free of charge if within a certain window from the initial test. Despite this, patients often cite cost as a barrier to undergoing testing. Concerns about insurance coverage are common after a positive result. The Genetic Information Nondiscrimination Act of 2008 prohibits discrimination against employees or insurance applicants because of genetic information. Life insurance or long-term care policies, however, can incorporate genetic testing information into policy rates, so patients should be recommended to consider purchasing life insurance prior to undergoing genetic testing. This is especially important if the person considering testing has not yet been diagnosed with cancer.

Implications of a positive result

Family members who receive a positive test result should be referred for genetic counseling and to the appropriate specialists for evidence-based screening and discussion for risk-reducing surgery (FIGURE).⁷ For mutations associated with hereditary breast and ovarian cancer, referral to breast and gynecologic surgeons with expertise in risk-reducing surgery is critical as the risk of diagnosing an occult malignancy is approximately 1%.²²

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Oncologists and genetic counselors may inaccurately assume that relatives of those undergoing cascade testing are being notified, and primary care providers may assume it is being taken care of by the oncology provider

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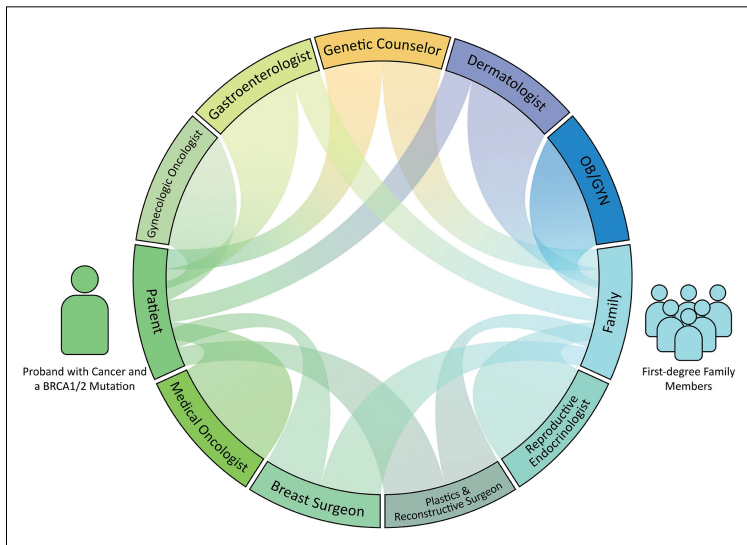


FIGURE Multidisciplinary care teams are required for both the patient with cancer and their first-degree family members to ensure evidence-based screening and prevention strategies are implemented for mutation carriers.

Patient resources: decision aids, websites

As genetic testing becomes more accessible and people are tested at younger ages, studies examining the balance of risk reduction and quality of life (QOL) are increasingly important. Fertility concerns, effects of early menopause, and the inter-relatedness between decisions for breast and gynecologic risk reduction should all be considered in the counseling for surgical risk reduction. Patient decision aids can help mutation carriers navigate the complex information and decisions.²⁵ Websites specifically designed by advocacy groups can be useful adjuncts to in-office counseling (Facing Our Risk Empowered, FORCE; Facingourrisk.org).

Family letters

The American College of Obstetricians and Gynecologists recommends an ObGyn have a letter or documentation stating that the patient’s relative has a specific mutation before initiating cascade testing for an at-risk family member. The indicated test (such as *BRCA1*) should be ordered only after the patient has been counseled about potential outcomes and has expressly decided to be tested.²⁶ Letters, such as the example given in the American College of Obstetricians and Gynecologists practice bulletin,²⁶ are a key component of communication between oncology providers, probands, family members, and their primary care providers. ObGyn providers should work together with genetic counselors and gynecologic oncologists to determine the most efficient strategies in their communities.

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Surgical technique with a 2-cm margin on the infundibulopelvic ligament and pathologic evaluation with sectioning and extensive examination of the fimbriated end of the tubes (SEE-Fim technique) is recommended for mutation carriers. Additionally, evidence has emerged suggesting an increased risk of uterine serous cancer in *BRCA1* carriers necessitating a discussion about risk-reducing hysterectomy in these patients.²³ Following risk reducing surgery, surgical menopause can have significant impacts on patients’ health and well-being. Treatment options including hormone replacement therapy can be considered.²⁴ To minimize recovery time burdens for patients, combination surgeries with breast, plastic, and gynecology specialties can be offered.

Summary of recommendations

Cascade, or targeted, genetic testing within families known to carry a hereditary mutation in a cancer susceptibility gene should be performed on all living first-degree family members over the age of 18. All mutation carriers should be connected to a multidisciplinary care team (FIGURE) to ensure implementation of evidence-based screening and risk-reducing surgery for cancer prevention. If gynecologic risk-reducing surgery is chosen, clinical trial involvement should be encouraged.

Technology

Access to genetic testing and genetic counseling has been improved with the rise in telemedicine. Geographically remote patients can now access genetic counseling through medical center-based counselors as well as company-provided genetic counseling over the phone. Patients also can submit samples remotely without needing to be tested in a doctor’s office.

Databases from cancer centers that detail cascade genetic testing rates.

As the preventive impact of cascade genetic testing becomes clearer, strategies to have recurrent discussions with cancer patients regarding their family members' risk should be implemented. It is still unclear which providers—genetic counselors, gynecologic oncologists, medical oncologists, breast surgeons, ObGyns, to name a few—are primarily responsible for remembering to have these follow-up discussions, and despite advances, the burden still rests on the cancer patient themselves. Databases with automated follow-up surveys done every 6 to 12 months could provide some aid to busy providers in this regard.

Emerging research

If gynecologic risk-reducing surgery is chosen, clinical trial involvement should be encouraged. The Women Choosing Surgical Prevention (NCT02760849) in the United States and the TUBA study (NCT02321228) in the Netherlands were designed to compare menopause-related QOL between standard risk-reducing salpingo-oophorectomy (RRSO) and the innovative risk-reducing salpingectomy with delayed oophorectomy for mutation carriers. Results from the non-randomized controlled TUBA trial suggest that patients have better menopause-related QOL after risk-reducing salpingectomy than

after RRSO, regardless of hormone replacement therapy.²⁷ International collaboration is continuing to better understand oncologic safety. In the United States, the SOROCK trial (NCT04251052) is a noninferiority surgical choice study underway for *BRCA1* mutation carriers aged 35 to 50, powered to determine oncologic outcome differences in addition to QOL outcomes between RRSO and delayed oophorectomy arms.

Returning to the case

The patient and her family underwent genetic counseling. The patient's 2 daughters, each in their 50s, underwent cascade genetic testing and were found to carry the same pathogenic mutation in *BRCA2*. After counseling from both breast and gynecologic surgeons, they both elected to undergo risk reducing bilateral salpingo-oophorectomy with hysterectomy. Both now complete regular screening for breast cancer and melanoma with plans to start screening for pancreatic cancer. Both are currently cancer free.

Summary

Cascade genetic testing is an efficient strategy to identify mutation carriers for hereditary breast and ovarian cancer syndrome. Implementation of the best patient-centric care will require continued collaboration and communication across and within disciplines. ●

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It is unclear which providers—genetic counselors, gynecologic oncologists, medical oncologists, breast surgeons, or ObGyns—are primarily responsible for follow-up discussions with patients, and the burden still rests on the cancer patients themselves

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