editorials

Emerging Opportunity of Cascade Genetic Testing for Population-Wide Cancer Prevention and Control

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Germline genetic testing is increasingly performed after a cancer diagnosis. The diffusion of more extensive genetic testing for hereditary cancer syndromes has accelerated into oncology practice for several reasons.[1] The technologic advances of next-generation sequencing, followed by a 2013 US Supreme Court decision against gene patenting, have shifted incentives toward inexpensive sequencing of multiple cancer-associated genes.[2,3] Furthermore, the indications for genetic testing are growing because the analytic validity is high, the clinical validity is rapidly improving, and there is evidence for clinical utility in several settings. The rapid uptake of tumor genomic sequencing has also facilitated companion germline testing.[4,5] The American Society of Breast Surgeons recently endorsed testing all patients with breast cancer for *BRCA1*, *BRCA2*, and *PALB2*, 3 high-penetrance breast cancer susceptibility genes,[6] and the National Comprehensive Cancer Network advises testing all patients diagnosed with epithelial ovarian cancer, pancreatic cancer, or metastatic prostate cancer, along with numerous other clinical scenarios.[7] Approximately 200,000 US patients diagnosed with cancer in 2020 are expected to undergo germline testing,[8-10] and this number will likely grow.

Although germline genetic testing informs cancer treatment, a primary goal is to enable precision cancer prevention and control. An evidence base has emerged to support practice guidelines for genetically targeted cancer risk reduction, encompassing prophylactic surgeries and intensified screening regimens including magnetic resonance imaging and endoscopy.[7,11] However, genetically targeted primary prevention requires testing people before a cancer diagnosis, and the logistics of such testing are controversial. Some call for population screening of all women for high-penetrance breast and ovarian cancer susceptibility genes,[12,13] but others question the clinical utility and safety of such a strategy, particularly given the shortfall of genetic experts and limited genetic knowledge among many clinicians.[14-17] There is more consensus in favor of a targeted cascade testing approach to an enriched subpopulation—the family members of patients with cancer found to carry pathogenic variants in clinically relevant cancer susceptibility genes—because first-degree relatives have a 50% probability of having inherited the same pathogenic variant.

In the article that accompanies this editorial, Offit et al[18] present a model-based analysis of widespread cascade genetic testing in the United States that supports this approach. The authors developed a multiple linear regression model to compare genetic testing approaches to identifying carriers of pathogenic variants in 18 clinically relevant cancer susceptibility genes, focusing on the time interval to detection of all US carriers with different utilization of cascade testing. They estimated that detection of all US carriers of pathogenic variants in these 18 genes would be completed within 9.9 years if there was 70% cascade testing of first-, second-, and third-degree relatives, compared with 59.5 years with no cascade testing.

As with any modeling exercise, the results of the study by Offit et al[18] are sensitive to the quality of the base case assumptions. Some of these assumptions are questionable, such as the assumption that patients with cancer treated at a US comprehensive cancer center routinely undergo germline sequencing of the 18 specified cancer susceptibility genes, with no stated assumption about genetic testing in other health care settings. A recent analysis of linked clinical genetic testing results and population-based SEER registry data demonstrated testing patterns that differ from such an assumption,[9] and thus, the actual time intervals would almost certainly vary from those predicted. Nonetheless, the study's striking result—6-fold faster identification of all US carriers of pathogenic variants in 18 clinically relevant cancer risk genes—makes a highly compelling case for increasing the uptake and depth of cascade testing to include all first-, second-, and third-degree relatives. The results from the study by Offit et al[18] are consistent with those of a previous model-based analysis of genetic testing for Lynch syndrome[19]; the number of unaffected relatives tested was a major determinant of the cost effectiveness of testing because primary cancer prevention offers the largest advantage in terms of life-years saved.

Despite these strong arguments favoring cascade testing, utilization studies reveal a major missed opportunity: less than half of at-risk relatives are tested in

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most series,[20-22] even though cascade testing is covered by insurance and endorsed by guidelines.[7,11,17] Several factors contribute to this gap. The fragmentation of the US health care system and insurance coverage contributes to suboptimal cascade testing; relatives largely receive care in different settings than the initially tested patient, and privacy regulations discourage direct outreach to relatives by the patient's clinician. Patients bear the primary responsibility for notifying and engaging their relatives about cascade testing[23-28] at a time when many are in the midst of arduous cancer therapy. Furthermore, the results of genetic testing are increasingly complex, including a substantial prevalence of variants of uncertain significance that are more common among racial and ethnic minorities and different clinical implications of pathogenic variants in a growing list of tested genes.[7,11,29,30] Given these barriers, it is not surprising that most at-risk relatives fail to receive cascade genetic testing and appropriate interventions targeted to their cancer risks. Thus, there is a great need to develop effective approaches to close the gap in cascade testing.

A second article in this issue addresses this need. Frey et al[31] present a feasibility study of 30 patients enrolled from a cancer genetics clinic at an academic medical center. Patients with a pathogenic variant identified relatives whom they permitted their genetics physician to contact by telephone, offering genetic counseling and saliva testing free of charge for the familial variant. A genetic counselor provided results disclosure and post-test counseling to relatives by telephone and sent management recommendations to the relatives' primary care physician. Seventy percent of relatives completed testing, with 6-month follow-up suggesting uptake of recommended screening and preventive interventions and low levels of testing or results-related distress. This successful pilot study offers encouraging evidence that direct outreach by the patient's clinicians can improve cascade testing of relatives, consistent with the results of similar studies in the United Kingdom and the Netherlands.[32,33]

However, although the high cascade rate of 70% is promising, several factors may limit the generalizability of the approach detailed by Frey et al.[31] The experience and resources of an academic cancer genetics program enabled the outreach to relatives reported by Frey et al.[31] Yet many US patients are tested without the benefit of genetics expertise,[3,34,35] and nongenetics clinicians may feel less confident in reaching out to relatives. Furthermore, genetic counselors and geneticists are in high demand and not reimbursed for telephone-based counseling and testing of relatives. Questions also remain about the ethics and legality of direct clinician outreach to relatives, particularly if patients are reluctant to share their genetic information.[23,36,37] In the study by Frey et al,[31] patients permitted their genetics physician to contact most of their relatives but declined contact of some as a result of a strained family relationship, the relative's medical illness, or other reasons. Notably, 29 of 30 enrolled patients were women, approximately half had attended college and the other half graduate school, and race and ethnicity were not reported. Prior studies have found that men, racial and ethnic minorities, and those with lower socioeconomic status are less likely to inform their relatives about genetic testing results,[25,28,32] which may hinder translation of this approach to more diverse populations and health care settings. In addition, although testing costs have declined markedly in recent years, testing and counseling relatives free of charge is unlikely to be feasible at scale. Thus, the study by Frey et al[31] demonstrates a best-case scenario achievable in a tertiary center of excellence, but alternative strategies for cascade genetic testing will be needed to serve the diverse patients and health care settings across the US population.

How can we bridge the gap from a single-institution feasibility study to widespread cascade genetic testing that extends to third-degree relatives? Although barriers to cascade testing are challenging, there are areas of substantial progress; the surge in genetic testing of patients with cancer has streamlined the identification of pathogenic variant carriers, and decreasing costs should make widespread testing of relatives increasingly feasible. Novel strategies are needed that cut across the wide variability in resources and practice context of US cancer care. One promising innovation is online, direct-to-relative testing initiatives[38]; yet questions remain about how best to deliver essential support with this approach, including personalized counseling about the meaning and implications of results and the next steps for reducing cancer risks. Broadly applied demonstration projects are needed to evaluate and optimize emerging care delivery models. There is also an ongoing need to identify barriers to cascade testing from the patient, clinician, and family perspectives, prioritizing vulnerable patient subgroups and less-resourced care settings. With recent progress in clinical cancer genetics, we now have an opportunity and an imperative to implement cascade testing as a path to population-wide cancer prevention and control.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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