

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 al¹⁸ 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 al¹⁸ 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 al¹⁸ are consistent with those of a previous model-based analysis of genetic testing for Lynch syndrome¹⁹; 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

ASSOCIATED CONTENT

See accompanying articles on pages 1389 and 1398

Author affiliations and support information (if applicable) appear at the end of this article.

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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 sub-optimal 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 testing²³⁻²⁸ 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 al³¹ 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 al³¹ 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 initiatives³⁸; 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 AND DATA AVAILABILITY STATEMENT

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REFERENCES

- Katz SJ, Kurian AW, Morrow M: Treatment decision making and genetic testing for breast cancer: Mainstreaming mutations. *JAMA* 314:997-998, 2015
- Offit K, Bradbury A, Storm C, et al: Gene patents and personalized cancer care: Impact of the Myriad case on clinical oncology. *J Clin Oncol* 31:2743-2748, 2013
- Kurian AW, Ward KC, Hamilton AS, et al: Uptake, results, and outcomes of germline multiple-gene sequencing after diagnosis of breast cancer. *JAMA Oncol* 4:1066-1072, 2018
- Stadler ZK, Schrader KA, Vijai J, et al: Cancer genomics and inherited risk. *J Clin Oncol* 32:687-698, 2014
- Mandelker D, Zhang L, Kemei Y, et al: Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. *JAMA* 318:825-835, 2017
- American Society of Breast Surgeons: Consensus guideline on genetic testing for hereditary breast cancer. <https://www.breastsurgeons.org/docs/statements/Consensus-Guideline-on-Genetic-Testing-for-Hereditary-Breast-Cancer.pdf>
- National Comprehensive Cancer Network: Guidelines for genetic/familial high-risk assessment: Breast and ovarian. Version 1.2020-December 14, 2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_bop.pdf
- Childers CP, Childers KK, Maggard-Gibbons M, et al: National estimates of genetic testing in women with a history of breast or ovarian cancer. *J Clin Oncol* 35:3800-3806, 2017
- Kurian AW, Ward KC, Howlander N, et al: Genetic testing and results in a population-based cohort of breast cancer patients and ovarian cancer patients. *J Clin Oncol* 37:1305-1315, 2019
- Gross AL, Blot WJ, Viswanathan K: BRCA1 and BRCA2 testing in medically underserved Medicare beneficiaries with breast or ovarian cancer. *JAMA* 320:597-598, 2018
- National Comprehensive Cancer Network: Guidelines for genetic/familial high-risk assessment: Colorectal. Version 3.2019-December 13, 2019. https://www.nccn.org/professionals/physician_gls/pdf/genetics_colon.pdf
- King MC, Levy-Lahad E, Lahad A: Population-based screening for BRCA1 and BRCA2: 2014 Lasker Award. *JAMA* 312:1091-1092, 2014
- Manchanda R, Patel S, Gordeev VS, et al: Cost-effectiveness of population-based BRCA1, BRCA2, RAD51C, RAD51D, BRIP1, PALB2 mutation testing in unselected general population women. *J Natl Cancer Inst* 110:714-725, 2018
- Delikurt T, Williamson GR, Anastasiadou V, et al: A systematic review of factors that act as barriers to patient referral to genetic services. *Eur J Hum Genet* 23:739-745, 2015
- Pal T, Cragun D, Lewis C, et al: A statewide survey of practitioners to assess knowledge and clinical practices regarding hereditary breast and ovarian cancer. *Genet Test Mol Biomarkers* 17:367-375, 2013
- Gray SW, Hicks-Courant K, Cronin A, et al: Physicians' attitudes about multiplex tumor genomic testing. *J Clin Oncol* 32:1317-1323, 2014
- Owens DK, Davidson KW, Krist AH, et al: Risk assessment, genetic counseling, and genetic testing for BRCA-related cancer: US Preventive Services Task Force recommendation statement. *JAMA* 322:652-665, 2019
- Offit K, Tkachuk KA, Stadler ZK, et al: Cascading after peridiagnostic cancer genetic testing: An alternative to population-based screening. *J Clin Oncol* 38:1398-1408, 2020
- Ladabaum U, Wang G, Terdiman J, et al: Strategies to identify the Lynch syndrome among patients with colorectal cancer: A cost-effectiveness analysis. *Ann Intern Med* 155:69-79, 2011
- Sharaf RN, Myer P, Stave CD, et al: Uptake of genetic testing by relatives of Lynch syndrome probands: A systematic review. *Clin Gastroenterol Hepatol* 11:1093-1100, 2013
- Roberts MC, Dotson WD, DeVore CS, et al: Delivery of cascade screening for hereditary conditions: A scoping review of the literature. *Health Aff (Millwood)* 37:801-808, 2018
- Menko FH, Ter Stege JA, van der Kolk LE, et al: The uptake of presymptomatic genetic testing in hereditary breast-ovarian cancer and Lynch syndrome: A systematic review of the literature and implications for clinical practice. *Fam Cancer* 18:127-135, 2019
- Knowles JW, Rader DJ, Khoury MJ: Cascade screening for familial hypercholesterolemia and the use of genetic testing. *JAMA* 318:381-382, 2017
- Finlay E, Stopfer JE, Burlingame E, et al: Factors determining dissemination of results and uptake of genetic testing in families with known BRCA1/2 mutations. *Genet Test* 12:81-91, 2008
- Cheung EL, Olson AD, Yu TM, et al: Communication of BRCA results and family testing in 1,103 high-risk women. *Cancer Epidemiol Biomarkers Prev* 19:2211-2219, 2010
- Daly MB, Montgomery S, Bingler R, et al: Communicating genetic test results within the family: Is it lost in translation? A survey of relatives in the randomized six-step study. *Fam Cancer* 15:697-706, 2016
- Dancyger C, Wiseman M, Jacobs C, et al: Communicating BRCA1/2 genetic test results within the family: A qualitative analysis. *Psychol Health* 26:1018-1035, 2011
- Fehniger J, Lin F, Beattie MS, et al: Family communication of BRCA1/2 results and family uptake of BRCA1/2 testing in a diverse population of BRCA1/2 carriers. *J Genet Couns* 22:603-612, 2013
- Hall MJ, Reid JE, Burbidge LA, et al: BRCA1 and BRCA2 mutations in women of different ethnicities undergoing testing for hereditary breast-ovarian cancer. *Cancer* 115:2222-2233, 2009
- Caswell-Jin JL, Gupta T, Hall E, et al: Racial/ethnic differences in multiple-gene sequencing results for hereditary cancer risk. *Genet Med* 20:234-239, 2018
- Frey MK, Kahn RM, Chapman-Davis E, et al: Prospective feasibility trial of a novel strategy of facilitated cascade genetic testing using telephone counseling. *J Clin Oncol* 38:1389-1397, 2020

32. Evans DG, Binchy A, Shenton A, et al: Comparison of proactive and usual approaches to offering predictive testing for BRCA1/2 mutations in unaffected relatives. *Clin Genet* 75:124-132, 2009
33. Sermijn E, Delesie L, Deschepper E, et al: The impact of an interventional counselling procedure in families with a BRCA1/2 gene mutation: Efficacy and safety. *Fam Cancer* 15:155-162, 2016
34. Katz SJ, Ward KC, Hamilton AS, et al: Gaps in receipt of clinically indicated genetic counseling after diagnosis of breast cancer. *J Clin Oncol* 36:1218-1224, 2018
35. Scott D, Friedman S, Telli ML, et al: Decision making about genetic testing among women with a personal and family history of breast cancer. *J Oncol Pract* 16:e37-e55, 2020
36. Rothstein MA: Reconsidering the duty to warn genetically at-risk relatives. *Genet Med* 20:285-290, 2018
37. Dheensa S, Fenwick A, Shkedi-Rafid S, et al: Health-care professionals' responsibility to patients' relatives in genetic medicine: A systematic review and synthesis of empirical research. *Genet Med* 18:290-301, 2016
38. Caswell-Jin JL, Zimmer AD, Stedden W, et al: Cascade genetic testing of relatives for hereditary cancer risk: Results of an online initiative. *J Natl Cancer Inst* 111:95-98, 2019



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