Low-Cost Online Cascade Test May Persuade Relatives to Investigate Their Own Cancer Risk

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—Kenneth Offit, MD, MPH

Although cascade testing can be a reliable gauge of whether close relatives of individuals with cancer also carry genetic mutations associated with the disease, experts have identified several barriers that prevent this strategy from being widely used. Potential hurdles include availability, the unwillingness of private insurance companies and Medicare to cover genetic testing for cancer-free individuals, and a patient’s own hesitancy to share a frightening diagnosis with relatives. An even bigger obstacle may be confidentiality: Many states have laws that prevent a patient’s physician or genetic counselor from alerting family members.

However, a low-cost online effort to overcome at least some of these barriers resulted in a substantial increase in the percentage of relatives of patients with cancer who underwent genetic testing, according to research from the Stanford University School of Medicine in Stanford, California, and recently reported in the *Journal of the National Cancer Institute* (published online ahead of print September 18, 2018. DOI:10.1093/jnci/djy147).

According to Jennifer L. Caswell-Jin, MD, a medical oncology instructor at Stanford and one of the lead authors, the study demonstrates that individuals who had a close relative with cancer-related mutations often were willing to be tested when contacted directly by a genetic testing laboratory and offered a low-cost test. “The online model we report on in this study breaks new ground as a novel way to improve access, allowing people who carry [cancer] risk mutations and their [first-degree] relatives to initiate testing and allowing the laboratory itself to contact relatives directly,” she says.

In recognizing the importance of cascade testing, the Centers for Disease Control and Prevention has designated it a tier 1 genomic application for *BRCA1/BRCA2* and Lynch syndrome, Dr. Caswell-Jin notes. “Cascade screening is one of the highest yield ways to identify people in the population with cancer risk mutations and could possibly reduce their risk of dying of cancer.”

“However, we are in the early days of figuring out how to implement cascade screening effectively,” she says. “Existing survey data suggest that only about one-third of eligible relatives of people with risk mutations who are seen in specialized genetics clinics get tested.”

**Study Details**
Working with Color Genomics, a genetics testing company based in Burlingame, California, the Stanford researchers evaluated a new family screening program in which patients who had pathogenic variants involving 1 of 30 cancer-associated genes were encouraged to provide e-mail addresses for their first-degree relatives. Color Genomics followed up by offering those on the list the opportunity to have their genes sequenced for $50, which is approximately 10% of what the tests typically cost.

The study ran from September 27, 2016, to September 27, 2017, and in that time a total of 1101 applicants invited 2280 first-degree relatives to undergo genetic testing. The majority of carrier applicants, 78.1%, were women, and female relatives also were more likely to submit to the tests than male relatives (52.6% vs 42.0%).

Of the invited relatives, 47.5% (95% CI, 45.5%-49.6%) underwent genetic testing. Thereafter, 12.0% of the invited relatives (95% CI, 9.2%-14.8%) who tested positive for the same
mutation as the original patient continued the cascade by inviting additional relatives to test. Of the tested relatives, 4.9% (95% CI, 3.8%-6.1%) were found to have a pathogenic variant in a different gene from the known familial one, and 16.8% (95% CI, 14.7%-18.8%) had a variant of uncertain significance.

**Study Implications**

The results of the study suggest that an online, low-cost program accomplishes 2 goals, Dr. Caswell-Jin says: 1) it attracts more potentially at-risk individuals to undergo cascade testing; and 2) it also may draw attention to unsuspecting individuals who carry a pathogenic variant in 1 of 30 cancer-associated genes.

Allison W. Kurian, MD, MSc, a senior author of the study and director of Stanford’s Women’s Clinical Cancer Genetics Program, says that although testing relatives for additional genes beyond the familial variant is not clinically recommended at this time, “This study assesses what would happen if this was done.” In addition, “Population screening as a strategy for identifying carriers of risk variants needs more study...[and these] results shed light on what might occur with population screening.”

“About 20% of these unexpected mutations were in high-risk genes (BRCA1/BRCA2 or Lynch syndrome), while the others were in emerging or lower risk genes,” says Dr. Kurian.

At the same time, she notes, “it is important to recognize that more work needs to be done.” For example, although individuals in the study model who tested positive spoke on the telephone with genetic counselors, researchers do not know whether they were able to access risk-reducing interventions. “Combining improved access, including via online approaches, with clinician expertise and guidance is going to be one of the key challenges and opportunities in cancer genetics,” she says.

According to Dr. Kurian, because the list of actionable cancer risk genes for which expert guidelines recommend changes in screening or risk reduction surgery is rapidly expanding, referral to expert genetic counseling is strongly recommended. “Clinicians should counsel their patients who carry risk variants in these genes about cascade testing. The person who carries the mutation must themselves notify their relatives, but the clinician can guide this process, including writing a letter for them to provide their relatives. Online tools such as the one we describe in this study can help to ease the process of cascade testing for carriers of risk variants, who often may be coping with a new cancer diagnosis simultaneously.”

Kenneth Offit, MD, MPH, chief of the clinical genetics service and vice chair of academic affairs in the department of medicine at the Memorial Sloan Kettering Cancer Center in New York City, agrees that easy access to testing for familial mutations is vital. “This study supports our own experience that cascade testing to family members is a powerful, cost-efficient, and scalable approach,” says Dr. Offit.

Dr. Offit, along with his colleagues at Harvard University in Boston, Massachusetts; the University of Pennsylvania in Philadelphia, Pennsylvania; and Cedars-Sinai Medical Center in Los Angeles, California, have been offering internet access to no-cost testing for BRCA mutations that are common in the Ashkenazi Jewish community (for more information, see BFORstudy.com). “We are finding in New York that many family members of those with known BRCA mutations have not been tested because they are too busy to see their doctor, but they also do not want to do a ‘spit and send’ test to a for-profit company with no medical support or assurance of privacy. Easier access to tests for genetic risk markers which run in families is a vital part of the practice of preventive medicine.”

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