Genetic Tests Create Treatment Opportunities and Confusion for Breast Cancer Patients

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The past decade has witnessed a rapid expansion of genetic tests, including new instruments to inform patients who have been diagnosed with breast cancer about the risk of recurrence and to guide their treatment.

But the clinical significance of many of the inherited mutations that can now be identified remains unclear, and experts are torn on when and how to deploy all the new tests available. Patients are sometimes left paying out-of-pocket for exams that are not yet the standard of care, and even the most up-to-date oncologists may be uncertain how to incorporate the flood of new information into what used to be standard treatment protocols.

A quarter-century ago, Myriad Genetics introduced the first breast cancer genetic test for BRCA mutations, two genes associated with a substantially elevated risk of getting breast cancer, opening the door to a new era in genetic testing. BRCA1 and BRCA2 mutations account for as many as half of all hereditary breast cancers, and people with a problematic mutation on one of those genes have a 45% to 72% chance of developing breast cancer during their lifetimes. They may also be at higher risk for ovarian and other cancers than people without harmful BRCA mutations.

But the clinical significance is murkier for many other genetic tests.

Testing for BRCA1 and BRCA2 genes used to cost thousands of dollars. Now, for a fraction of that, doctors can order multi-gene test panels from commercial labs that look for mutations in dozens of genes. Some direct-to-consumer companies offer screening panels for a few hundred dollars, though their reliability varies.

When Jen Carbary was diagnosed with breast cancer in 2017 at age 44, genetic testing identified a mutation in a gene called PALB2 that significantly increases the risk of developing breast cancer. Guidelines suggest that breast cancer patients with a PALB2 mutation, much like those with BRCA1 and BRCA2 mutations, consider having a mastectomy to reduce the chance of a breast

cancer recurrence.

“I wish genetic testing was the standard of care,” said Carbary, who owed nothing for the test because her insurer covered the cost.

Carbary, who lives in Sterling Heights, Michigan, said the test results affirmed the decision she had already made to have a double mastectomy and provided important information for family members, including her 21-year-old daughter and 18-year-old son, who will likely be tested in their mid-20s or early 30s.

But some breast cancer experts are concerned that widespread testing may also identify genetic mutations whose impact is unclear, creating anxiety and leading to further testing and to treatment of questionable value that could raise costs for the health care system.

It can also confuse patients.

“It happens a lot, that patients find their way to us after getting confusing results elsewhere,” said Dr. Mark Robson, chief of the breast medicine service at Memorial Sloan Kettering Cancer Center in New York City. Robson said the cancer center has a clinical genetics service, staffed by doctors and genetic counselors, that helps people make decisions about how to manage genetic testing results.

For people diagnosed with breast cancer, many professional groups, including the influential National Comprehensive Cancer Network, or NCCN, recommend limiting testing to certain people, including those with high-risk factors, such as a family history of breast cancer; those who are 45 or younger when they’re diagnosed; and those with Ashkenazi Jewish ancestry.

But in 2019, the American Society of Breast Surgeons recommended a different approach: Offer genetic testing to all patients who are diagnosed with or have a personal history of breast cancer. The recommendation was controversial.

“The NCCN guidelines [cover] most of the women who needed testing, but we wanted to get them all,” said Dr. Eric Manahan, a general surgeon in Dalton, Georgia, and a member of the surgeons group’s board of directors.

Mutations on other genes that are associated with breast cancer are much less common than BRCA1 and BRCA2 mutations and generally don’t increase the risk of developing breast cancer as much. The cancer-causing impact of these genes may be less clear than that of the BRCA genes, which have been tested for since the mid-1990s.

And the appropriate response to the less common mutations — whether to consider a risk-reducing mastectomy or stepped-up screening — is often unclear.

“Things get sloppier and sloppier when you look at other genes,” said Dr. Steven Katz, a professor of medicine and health management and policy at the University of Michigan. “The risks tend to be

lower for different cancers, and less certain and more variable. You might walk away wondering, 'Why'd I have to know that?'"

After people are diagnosed with breast cancer, genetic testing can help inform their decisions about the types of surgery to pursue — for example, a high risk of recurrence or a new breast cancer might persuade some to opt for more extensive surgery, such as a double mastectomy. Testing can also provide important information to family members about their potential cancer risk.

(This type of "germline" genetic testing, as it's called, looks at mutations in the genes that people inherit from their parents. It is different from genomic tumor tests that look at specific genes or proteins in the cancer cells and can help doctors understand the rate at which the cancer cells are dividing, for example, and the likelihood of a cancer recurrence.)

Increasingly, germline genetic testing can also help guide other treatment decisions. Some patients with metastatic breast cancer who have BRCA1 or BRCA2 mutations may be good candidates for PARP inhibitors, cancer drugs that target tumors with mutations in those genes.

But genetic testing that uncovers inherited mutations in many other genes yields less clearly actionable information, even though positive results may alarm people.

At Memorial Sloan Kettering, cancer specialists focus on "therapeutic actionability," said Robson. Will testing help someone decide whether she should get a double mastectomy or provide other important guidance? "A policy of testing everyone will identify very few additional BRCA breast mutations but will cost a lot," he said.

As a result, doctors are debating how best to deploy and incorporate new genetic knowledge. Insurers are trying to figure out which to pay for.

There is both underuse of tests that science says are relevant and overuse of tests that experts say provide information that can't be interpreted with any scientific certainty.

The result may be confusion for patients newly diagnosed with breast cancer as they confront the expense of genetic tests and sometimes little guidance on the proper treatment.

Some doctors say the first step is to make sure that the small group of people who would clearly benefit are getting the genetic tests whose meaning is clearly understood. Only 15% of breast cancer patients who met select NCCN testing guidelines for inherited cancer received genetic testing, according to a 2017 study that examined data from a national household health survey between 2005 and 2015.

"I would argue that our focus needs to be on the people who are at high risk for breast cancer that aren't even identified yet," said Dr. Tuya Pal, associate director for cancer health disparities at Vanderbilt-Ingram Cancer Center and vice chair of the NCCN guidelines panel for genetic/familial high-risk assessment of breast, ovarian, and pancreatic cancers.

Patients may fall through the cracks because no one tells them they should be tested. In one analysis, 56% of high-risk breast cancer patients who didn't get genetic testing said their doctors didn't recommend it.

Even if doctors recommend genetic testing, they may lack the expertise to determine which tests people need and how to interpret the results. That's the role of genetic counselors, but their ranks are stretched thin.

The consequences can be serious. In a study of 666 breast cancer patients who received genetic testing, half of those at average risk for inherited cancer got double mastectomies based on test results that found "variants of uncertain significance," which aren't clinically actionable. As many as half of surgeons reported managing such patients the same way as those with cancer-causing mutations.

"The bulk of our research would say that there is still room for improvement in terms of clinicians getting the understanding they need," said Dr. Allison Kurian, director of the women's clinical cancer genetics program at Stanford University and a co-author of the study.

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