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HEALTH

Finding Risks, Not Answers, in Gene Tests

By **DENISE GRADY** and **ANDREW POLLACK** SEPT. 22, 2014

Jennifer was 39 and perfectly healthy, but her grandmother had died young from breast cancer, so she decided to be tested for mutations in two genes known to increase risk for the disease.

When a genetic counselor offered additional tests for 20 other genes linked to various cancers, Jennifer said yes. The more information, the better, she thought.

The results, she said, were “surreal.” She did not have mutations in the breast cancer genes, but did have one linked to a high risk of stomach cancer. In people with a family history of the disease, that mutation is considered so risky that patients who are not even sick are often advised to have their stomachs removed. But no one knows what the finding might mean in someone like Jennifer, whose family has not had the disease.

It was a troubling result that her doctors have no idea how to interpret.

Such cases of frightening or confusing results are becoming more common because of a big recent change in genetic testing for cancer risk. Competing companies have hugely expanded the array of tests they offer, in part because new technology has made it possible to sequence many genes for the same price as one or two. Within the next year, at least 100,000 people in the United States are expected to undergo these tests. The costs, about $1,500 to $4,000, are covered by some, but not all, insurers.

The new tests build on the success of earlier ones for inherited risks of breast, ovarian and colon cancer, which can give people options for prevention, like getting screened more often, taking a drug to lower breast

cancer risk, or having their breasts or ovaries removed.

But some doctors worry that the newer tests for up to 30 genes may open a can of worms, because the ability to find mutations has outpaced the understanding of what they mean. In some cases, tests find cancer-associated mutations for which there are no preventive measures, and the patient is left with a bleak prognosis.

Some genes were included "because they could be tested, not necessarily because they should be," said Dr. Kenneth Offit, chief of clinical genetics at Memorial Sloan Kettering Cancer Center in New York. He said that the testing companies are "rushing headlong into this era," and that "individuals are getting results we're not fully educated to counsel them on."

The emergence of multigene testing was accelerated by a Supreme Court ruling last year. Before that, starting in the 1990s, almost all testing for hereditary breast cancer risk was done by Myriad Genetics, which had patents covering two genes, BRCA1 and BRCA2. Mutations in these two genes significantly increase risk.

But the Supreme Court invalidated key patents on the BRCA genes. Numerous companies like GeneDx, Ambry Genetics, Invitae and Quest Diagnostics quickly began offering BRCA tests, and many tried to get a jump on Myriad by offering multigene panels, rather than just BRCA testing.

To keep pace, Myriad introduced its own test of 25 genes linked to various types of cancer, for about the same $4,000 price as the BRCA-only test. The company expects to do 100,000 of the new tests in the next year or so. It has been doing 250,000 BRCA tests per year, but says it plans to stop offering BRCA-only risk tests by next summer, in favor of the panel.

Some people who have multiplex tests, like Jennifer, are worried about one disease but get blindsided by results pointing to another. Dr. Offit said he had seen two other patients with the same test results as Jennifer in the past few months.

In many other cases, a mutation is found but there is little or no data on whether it raises the risk of getting cancer. In some versions of the new multigene tests, more than 30 percent of patients will be told they have such

mutations, which are called “variants of unknown significance.”

“Patients are not getting closure,” Dr. Offit said. “They’re walking out not knowing what to make of it.”

Dr. Susan Domchek, an expert on breast cancer mutations at the University of Pennsylvania, said: “With panels, only about 10 percent of the time do we find a clear mutation in anything, and even when we do we’re not exactly sure how we should change management. But sometimes we do.”

Mary-Claire King, a professor of medicine and genome sciences at the University of Washington who helped discover the BRCA1 gene, said that laboratories should not even report variants of unknown significance to doctors and patients.

“We need to report back only what is devastating and clearly devastating,” she said. “Patients and their physicians need to have information that they can act on and they can act on with clarity.”

She said the vast majority of such uncertain variants would turn out to be benign anyway, so there was little reason to worry people, especially when that might motivate them to have prophylactic surgery.

But Dr. King conceded that most experts do not agree with her about withholding uncertain findings.

A recent study in the journal Cancer showed the pros and cons of multigene testing. It used Myriad’s 25-gene test to examine nearly 1,800 people who were referred for BRCA testing because they had breast cancer.

As expected, about 9.3 percent had BRCA mutations. Another 3.9 percent had a mutation in a different gene related to breast or ovarian cancer, and 0.3 percent had a mutation in a gene linked to other cancers. Some of the non-BRCA findings were serious, and warranted advising patients to consider preventive surgery, the researchers said.

There was a considerable downside: Variants of unknown significance were identified in more than 41 percent of the patients. Some patients had more than one. Almost all were in genes that, unlike BRCA1 and BRCA2, had not been studied extensively. Doctors have no advice for such patients, except to wait until more is known.

Experts say that over time, as more people are tested, more is learned about mutations, and the rate of uninterpretable variants should decline. When Myriad began BRCA testing, its rate of unknown variants was 40 percent. Now it is 2 percent.

Various efforts are underway to interpret mutations and compile them in publicly available databases; one of the latest is an online registry to which patients can upload their own data. Eventually, they will be able to see how many other people have the same mutation, and how many get cancer. Called Prompt, for Prospective Registry of Multiplex Testing, it was created by Memorial Sloan Kettering, the University of Pennsylvania, the Mayo Clinic and the Dana-Farber Cancer Institute. Several genetic testing companies are also helping to promote it.

Jennifer said she was eager to join, mainly to make sure her mutation was better understood, in case her two young children have it. She lives in New York, and asked that her last name be withheld to protect her family's privacy.

In the meantime, no one is suggesting that she have her stomach removed. But she has been advised to have an endoscopy — a procedure in which a camera-tipped tube is passed into the stomach to examine it — twice a year, probably for the rest of her life. Her mutation may also be linked to breast cancer, so she will be consulting specialists about screening.

Tamika Matthews, 40, from the Bronx, has had breast and thyroid cancer, and has had both breasts removed. Her genetic tests found no BRCA mutations, but did detect variants of unknown significance in four genes that may be linked to cancers, including those of the colon and breast. She had no family history of breast cancer, but her grandmother and two great-aunts had colon cancer.

"When they called me in and gave me the results, I wanted to say, 'Please, I don't want to know everything. I changed my mind,' " Ms. Matthews said. "But it's better to be informed."

But what has she been informed of?

"It's so up in the air," she said. "But I'm glad somebody's working on it, at least."

Ms. Matthews has a son, 19, and hopes the registry will turn up information that will help him.

"Even though he may not get breast cancer, he may have daughters," Ms. Matthews said. "I don't want them to go through what I went through."

Correction: September 26, 2014

An article on Tuesday about genetic testing for cancer risk referred incorrectly at one point to the role that the genes BRCA1 and BRCA2 play in breast cancer. As the article correctly noted elsewhere, mutations in these genes, not the genes themselves, increase the risk of breast cancer.

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