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# *Don't Count on 23andMe to Detect Most Breast Cancer Risks, Study Warns*

By **Heather Murphy**

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In 2010, Dr. Pamela Munster mailed her saliva to 23andMe, a relatively new DNA testing company, and later opted in for a BRCA test. As an oncologist, she knew a mutation of this gene would put her at high risk for breast and ovarian cancer. She was relieved by the negative result.

Two years later, after she learned she had breast cancer, she took a more complete genetic test from a different lab. This time it was positive.

A study of 100,000 people released earlier this month suggested that this experience could be widespread. Nearly 90 percent of participants who carried a BRCA mutation would have been missed by 23andMe's test, geneticists found.

23andMe's testing formula for this risk is built around just three genetic variants, most prevalent among Ashkenazi Jews. The new study demonstrated that most people carry other mutations of the gene, something many doctors have long suspected.

"It's as if you offered a pregnancy test, but only the Jewish women would turn positive," said Dr. Munster, who is the co-leader of the Center for BRCA Research at the University of California, San Francisco. She was not involved in the new study, which was conducted by Invitae, a diagnostic company.

23andMe said response to the study by its potential competitor had been overblown because the site makes it clear that it is testing only for three of the mutations.

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Dr. Munster said that 23andMe was "not doing anything actively deceptive." But she is still concerned that many customers do not grasp the limits of mail-in genetic testing.

23andMe now has more than 10 million customers. Even if only a small percentage take the test, that's thousands who could be misled.

Mary-Claire King, a professor at the University of Washington who discovered the region on the genome that became known as BRCA1, had a more blunt assessment of the Food and Drug Administration's decision to allow the test.

“The F.D.A. should not have permitted this out-of-date approach to be used for medical purposes,” Dr. King said. “Misleading, falsely reassuring results from their incomplete testing can cost women’s lives.”

## How was the study conducted?

The study, which was presented at the American College of Medical Genetics and Genomics annual meeting and has not been peer reviewed, was built around more than 100,000 patients who underwent breast cancer risk testing with Invitae, a diagnostic company.

Despite the lack of peer review and Invitae’s potential role as a business competitor, genetic medicine experts not affiliated with Invitae said in interviews that they found the work to be credible, particularly as the company’s findings echo other, smaller studies.

23andMe’s test focuses on BRCA1 and BRCA2, genes involved in suppressing growth of abnormal cells. Specifically, it looks for three notorious genetic variants, known as founder mutations. Invitae’s analysts expanded their search to include thousands of other variants.

Dr. Susan Klugman, vice president for clinical genetics at the American College of Medical Genetics and Genomics, likened it to a broader spell-check. Whereas 23andMe looks for errors in a few paragraphs, the Invitae analysts used more advanced genetic technology to search through 25 chapters. (Dr. Klugman was not involved in the Invitae study.)

In about 5,000 subjects, analysts identified at least one variant known to significantly increase an individual’s risk of breast and ovarian cancer. Among the Ashkenazi Jews in the positive group, 81 percent had one of the three founder mutations, suggesting that 23andMe’s test could be helpful for them. Among the rest, 94 percent carried variants that would have failed to be detected by 23andMe.

## Why create a test that misses so many people?

One reason is purely technical: To return to the literary metaphor, 23andMe isn’t set up to scan entire genetic books the way some labs are. So even if the company wanted to look for other variants, that would not be possible without changing its approach, said Dr. Robert C. Green, a professor at Harvard Medical School.

Dr. Green said that limitation is not necessarily a problem.

“I think people have the right to their own genetic information, but with that right comes a responsibility,” he said. “If you are going to go around the medical mainstream, read the caveats.”

Dr. Jeffrey Pollard, 23andMe’s director of medical affairs, said that the company’s focus was far from arbitrary.

“We test for these three variants since they are three of the most well-studied and carry clear, documented risk for breast and ovarian cancer,” he said. “About one in 40 individuals of Ashkenazi Jewish descent has one of these three variants. Women with one of these variants have a 45 to 85 percent chance of developing breast cancer by age 70.”

The company warns customers that it is not testing for all variants, and its approach has been approved by the F.D.A., he said. (The company said that data on how many people have taken its test was not available.)

## **Do online genetic tests also give false positives?**

Yes. Alongside the primary study, Invitae analysts also presented a smaller study investigating this question, built around 102 patients. All participants had been told that they had a mutation of the gene from a mail-in test or other online analysis service. (Whether they used 23andMe or another service was not documented. Based on their reading of the data, 23andMe analysts insisted their company’s results were not a part of the study.)

In nearly half of the patients, Invitae could not confirm the presence of a mutation. That means that had these patients not taken a second test, they would have gone on thinking that they were at greater risk for inherited cancer than they really were.

A positive result can be a major life event: Some people may opt to get a preventive mastectomy or hysterectomy. Others may increase the frequency of their doctors’ visits or alter other habits.

Another small study published last year produced similar results for other inherited illnesses. Forty percent of individuals who tested positive for genetic variants associated with Parkinson’s disease, late-onset Alzheimer’s disease and a number of other diseases using mail-in genetic tests were negative in a confirmation test.

## **So why offer online genetic health tests?**

One of the primary arguments for genetic testing that does not involve a physician is that it reaches people who would not do it otherwise. Around one in 25 American adults has now taken an at-home ancestry test.

Regardless of who does the test, talking to a genetic counselor or medical geneticist is advisable, Dr. Klugman said. Genetic counselors can help patients make sense of their results, and sometimes they sniff out incorrect findings.

In 2017, for example, a genetic counselor was skeptical of tests showing that two patients from a family with a history of Lynch syndrome, which increases the risk of several types of cancer, did not carry the mutation. Retesting showed they did.

In that case, the faulty results could not be blamed on a mail-in test: Invitae, the company behind the recent studies, produced the incorrect results. In an email last week, the company said that it had corrected the reports and learned from the mistake.

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