



## GENETICS

## DNA Test for Breast Cancer Risk Draws Criticism

It's been 8 years since the human genome was sequenced with the promise of revolutionizing medicine, and since then, efforts to put DNA discoveries into the doctor's office have only grown more controversial. The latest tussle came last week after deCODE Genetics, an Icelandic company, released the first-ever breast cancer risk test designed to cover common forms of the disease. The rollout and reaction were predictable: deCODE hailed the test as offering women a chance to take advantage of more aggressive screening if they're found at higher risk. Many oncologists and geneticists decried the \$1625 test as premature because it includes just seven genetic variants out of the dozens or hundreds driving breast cancer that scientists expect to find soon.

Unlike some new genetic tests, this one is not in question over its science: The seven variants it uses, all single-nucleotide polymorphisms (SNPs) found in the last couple of years, have been linked to an increased risk of breast cancer in thousands of women, mainly of European descent. Five of the variants were identified by a group at the University of Cambridge, U.K., using genome-wide association. These SNPs are in the public domain, and companies can incorporate them into new products.

The test does not check for mutations in *BRCA1* and *BRCA2*, two genes that dramatically increase the risk of breast cancer. Those mutations are rare, accounting for only a small fraction of cases, and they have been patented by a company in Utah that holds exclusive rights to test for them in the United States.

The quandary presented by deCODE's breast cancer test, its sixth genetic risk test for a common disease, reflects a broader puzzle in genetics. Each new disease-linked SNP scientists uncover confers only a slight increase in risk, often no more than 20%. That might boost someone's lifetime chance of a chronic disease from 8% to 10%, so small as to be of questionable use to an individual. Even having several of these SNPs isn't likely to increase risk more than 100%, which amounts to a doubling. For breast cancer, that's roughly equivalent to having

one family member with the disease.

Whereas some argue that such information isn't robust enough for clinical use, others see no reason to hold off. "It goes against our tradition to say, 'Let's wait until we discover more,'" says Kári Stefánsson, a neurologist and the chief executive officer of deCODE. The risk his test uncovers, he

drug taken to prevent breast cancer, based on the deCODE test results, though he hasn't done that yet.

Others are more wary. "Any test, even based on the best SNPs so far, will probably misclassify a substantial fraction of women," says David Hunter, a genetic epidemiologist at Harvard School of Public

Health in Boston. That's because many believe the genetic risk identified in DNA so far is only a few percent of what will eventually be discovered. "Women need to know that their risk estimates might actually change over time as more variants become available," Hunter adds, noting that some labeled high-risk may later learn that the news isn't so bad, or vice versa.

"What you're seeing is someone's risk based on a small subset of variants," agrees Douglas Easton, a genetic epidemiologist at the University of Cambridge in the U.K. who led the team that identified five breast cancer SNPs last year. "You don't

know what the whole hand is."

Mitchell Gail, a medical statistician at the National Cancer Institute in Bethesda, Maryland, who designed a commonly used breast cancer risk model, earlier this year analyzed how much risk predictions would be strengthened by testing for most of the SNPs in deCODE's test. (Predictions are now based on factors such as family history.) "I'm not seeing a lot of improvement," says Gail, who published his analysis in July. He estimates that about 300 SNPs are needed to dramatically improve risk forecasts for breast cancer.

Stefánsson finds such arguments infuriating. "They basically say we should wait until we have discovered everything about breast cancer," he says of his colleagues. "That is somewhere between ridiculous and incredibly dangerous." —JENNIFER COUZIN



**Tipping point.** A \$1625 genetic test will inform women if they're at high enough risk to merit MRI screening for breast cancer, the manufacturer says.

argues, is meaningful: Published work suggests that about 5% of women who use the company's test will find that they have a 20% risk of breast cancer; average risk is just over 12%. At 20% risk, U.S. guidelines recommend additional screening using magnetic resonance imaging (MRI).

"This is a suitable test for anyone," says Owen Winsett, a surgeon and director of the Breast Center of Austin in Texas. Winsett contacted deCODE last spring after learning about its work, and the company quotes his favorable comments in its press release. Winsett, who says he has not received any compensation, is backing his words with action. In the last month, he has offered the test to about 25 patients worried about breast cancer and recommended regular MRIs for some based on the results. Winsett says he would support prescribing tamoxifen, a