

Unraveling Your DNA's Secrets

Do-it-yourself genetic tests promise to reveal your risk of coming down with a disease. But do they really deliver?

By Nancy Shute

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Ellen had long thought that her death was preordained. Her mother and aunt died of ovarian cancer, and her mother had breast cancer, too. So the 54-year-old woman decided to get tested for the BRCA genes that cause hereditary breast and ovarian cancer. "I wanted to do the testing anonymously," she says. "I didn't want it in my medical records." First Ellen called Myriad Genetics, the Salt Lake City outfit that holds the patent on the BRCA genetic test. But Myriad wouldn't test her without a doctor's signature, and her doctor would only sign if she used her real name. (Ellen is an alias.) Then she heard about DNA Direct, a San Francisco firm that sells the test to the public. Under an assumed name, Ellen took the test in June, and it came back positive for the BRCA mutation.

Genetic testing is getting faster and cheaper. Many tests require only a painless cheek swab to obtain your DNA.

CHARLIE ARCHAMBAULT FOR USN&WR

Ellen, who lives in New York, kept mum as she bought long-term care insurance and increased her life insurance. "Those were a hard three months," she says now. "I was convincing myself that I really had something." She finally told her doctor, and in early December, she had surgery to remove her ovaries, the only way to ensure that she won't get ovarian cancer. Now she's talking with an oncologist and a reconstructive surgeon about having her breasts removed. "I'm very happy with DNA Direct," she says. "They did excellent medical and genetic counseling."

In an era of inexpensive DNA analysis, genetic testing has become absurdly simple: Buy a test online, and within a few days a kit arrives in the mail. Rub the small brush on the inside of your cheek for 30 seconds, pop it back in the prepaid envelope, mail it back, and voilà! In a short time, you'll receive the truth about your genes. "A lot of people didn't have access to these tests," says Ryan Phelan, an entrepreneur who founded DNA Direct in 2003 to sell tests for cancer, cystic fibrosis, and other diseases. "This started really out of seeing a very important need," Phelan says. "And if there's a need for it, maybe there's also a good business."

Real genes. But is good business also good medicine? In the past few years, dozens of companies have started selling genetic tests via the Internet. Some are real medical tests, for diseases including breast cancer, celiac disease, and

hemochromatosis. Others test real genes but don't give information that's useful in making personal health decisions. "Many of the claims that are being made are quite fanciful," says Francis Collins, director of the National Human Genome Research Institute, who oversaw the project to sequence the human genome. "But the fact that many of these tests have not yet reached the point of rigorous scientific validation has not slowed down the interests of consumers and of entrepreneurs."

For years, scientists have predicted that medical care will improve as they decode the ties between genes and disease. Just about every week there's a "disease gene" discovery. But so far, very few genes associated with major diseases have proved helpful in diagnosis or treatment. A few genetic tests are used for diagnosing familial breast and colon cancers. Others are helpful in tailoring cancer treatments.

The first big application of genetics for medical treatment, which the Food and Drug Administration is considering, will be for warfarin, a blood thinner prescribed to prevent strokes. The test identifies patients who have trouble metabolizing standard doses of the drug, which can lead to bleeding in the stomach or brain. "The genetic test is the most powerful indicator of where to start the dose," says Michael Watson, who directs the American College of Medical Genetics. "What is much less clear is whether it would reduce the number of bleeding problems." In 2004, the ACMG said that at-home genetic tests are potentially harmful. But it is reassessing that stance, says Watson, as it believes some forms, such as carrier screening, are less problematic.

To investigate the quality and usefulness of direct-to-consumer genetic tests, U.S. News tried six of them. Three were the same type of tests used by doctors for celiac disease, hemochromatosis, and breast cancer. Three others—for Alzheimer's disease, depression, and glaucoma and macular degeneration—test genes associated with the diseases but aren't used in medical practice. Our testers were U.S. News staff members and their relatives. One staffer took a DNA sample from his 3-year-old dog, Tate, a corgi mix. We found that the value in diagnosing or predicting disease varies widely. Some could be helpful in making health decisions, while others could be worthless or even dangerous. And it's often hard to tell which is which. Our key findings:

Some tests that promise to reveal the risk of disease rely on genes that aren't up to the task. The gene tested for Alzheimer's disease, for example, indicates only increased susceptibility. And there's nothing people can do to reduce that risk.

The advice some testing firms offer patients with the results can be misleading. The test results often overstated the risk of disease or were unclear about how to interpret that risk. References to scientific research included with some of the

results were outdated or irrelevant. Several tests offered generic preventive advice, such as "get regular exercise." Just two companies, DNA Direct and Denver's Kimball Genetics, offered access to certified genetic counselors trained to interpret and explain the results. Experts in the field say that interpretation is crucial because the results are usually not black and white.

Direct-to-consumer genetic tests are not regulated. The FDA does not evaluate the safety and efficacy of at-home genetic tests. Some are done in certified laboratories used by doctors and hospitals; others are not. In July, the Federal Trade Commission urged consumers to be wary of the claims of DTC genetic testing.

Although there are now more than 900 genetic tests available to doctors, most are used to screen for rare disorders like Duchenne muscular dystrophy. For decades, scientists have been hunting similar triggers for killers like heart disease and cancer. What they've found are dozens of genes that interact with one another—and with environmental effects like smoking. For instance, women with mutations in BRCA genes have an 84 percent chance of getting cancer. But then again, there's a 16 percent chance they won't.

Until now, most people who encountered genetic testing were expectant women, who are routinely offered screening to see if they're carriers of the genes for cystic fibrosis, sickle cell anemia, or Tay-Sachs. Amniocentesis and chorionic villi sampling tests can reveal genetic disorders in a fetus. Newborns are screened for dozens of genetic disorders like phenylketonuria, a metabolic disease, which are treatable if detected early. Preimplantation genetic diagnosis is increasingly being used to screen embryos for fatal disorders—and also to pick the child's sex.

So if embryos can have a molecular crystal ball, why not grownups? Alas, using genetic tests to predict eventual disease is a lot tougher than diagnosing if the person already has a disease. "It could account for the disease, or maybe it can't," says Georgia Wiesner, a geneticist at Case Western Reserve University. "There could be other genes or other factors." With only a few diseases caused by a single gene, like Huntington's disease, is it certain that a person who tests positive will succumb.

Future peek. Still, there's no question that many people find the chance to peek into the medical future irresistible. Unfortunately, three of the tests that we analyzed that are marketed as gauging the risk of major diseases relied on genes that don't provide a clear view. The Alzheimer's test, sold for \$150 by Graceful Earth of Honolulu, examines the APOE gene. One version is associated with an increased risk of Alzheimer's. Our tester, a 41-year-old female, was told that she had APOEe3. Not having APOEe4, the test results said, offered "moderate protection" from Alzheimer's. But half of people with Alzheimer's don't have

APOEε4, and many people with it will never get Alzheimer's. "It doesn't have a lot of value to the patient," says William Thies, vice president of medical and scientific affairs for the Alzheimer's Association, which recommends against using APOE for predictive testing. Kenneth Friedenberg, vice president of Graceful Earth, agrees that having APOEε4 doesn't mean that someone will get Alzheimer's. "We've gotten criticism from doctors," he says. "But I think people really want to know, especially if they'd had it in their family." Knowing a person is at increased risk, he says, could prompt him or her to eat healthier. "What is the harm if someone starts increasing their intake of antioxidants? Or fish oils? How is that going to hurt them?"

Depression is another serious disease, estimated to affect 1 in 10 Americans. A depression risk test, sold by NeuroMark of Boulder, Colo., for \$125, says it tests for variations in a serotonin transporter gene, 5-HTTLPR. In 2003, researchers found that people with one version of the gene were more likely to become clinically depressed after stressful events. Our tester, a woman in her 50s with a family history of depression, was told she had a variant that makes her less susceptible. But 5-HTTLPR is only one of dozens of genes that may play a role in depression. And five years from now, the genes linked to depression will probably be totally different from those on the list now, says Douglas Levinson, a professor of psychiatry at Stanford University who is leading a huge national hunt for depression genes. Knowing those genes may also make it easier to identify nongenetic factors. Studies on twins, for example, suggest that about half of depression is caused by genes, the other half by the environment. "Are there some people for whom it's almost entirely genes? And others it's not genes?" asks Levinson. "We just don't know."

NeuroMark says the purpose of the test is "educational," and it is not attempting to assist doctors in diagnosing depression. "That would be a reach," says CEO Kim Bechthold, who notes the firm no longer sells the depression test because of "enormous demand." It plans to reintroduce the test in mid-2007.

Fear of disease is a powerful motivation to seek out genetic testing, and that's certainly the case with blindness. Age-related macular degeneration and glaucoma are two leading causes in people over age 55. Macular degeneration causes deterioration in the retina; with glaucoma, excess pressure within the eye damages the optic nerve. A test for macular degeneration and glaucoma, sold for \$99.95 by CyGene Laboratories of Coral Springs, Fla., looked at three variants in the myocilin gene. But those are just three of the 80 to 100 myocilin changes associated with glaucoma. Our tester, a 37-year-old woman with abnormally high pressure on glaucoma tests, got this news: "You do not have an increased risk for developing Primary Open Angle Glaucoma over the general population." That may or may not be true. "It's just too small a slice," says Janey Wiggs, an ophthalmologist at Harvard Medical School who is leading a national study of the

genetics of glaucoma. "You could easily miss a mutation that could be related to very severe glaucoma." So far, Wiggs says, genetic testing is useful only in patients with early onset of glaucoma and a family history of the disease, something that our tester doesn't have. The best way to screen for disease, Wiggs says: Go to the eye doctor. Martin Munzer, CEO of CyGene, says that "we could do a comprehensive vision panel, but nobody would be able to afford it." His company's test, he says, is not definitive, but "it's like chicken soup—it won't hurt you." He agrees that regular eye exams are the best screening tool.

When considering do-it-yourself genetic testing, customers need to be certain the tests are performed properly. "People should be aware that there is no regulation of the quality of the tests that are being sold over the Internet," says Kathy Hudson, director of the Genetics and Public Policy Center at Johns Hopkins University. "They may not be certified labs, and even if they are, the regulations for laboratory quality really are general and have minimal standards. They don't assess whether a laboratory is able to accurately do genetic tests."

The FDA, which approves drugs and medical devices, deems genetic tests "services," devised by the labs that perform them. And the Centers for Medicare and Medicaid Services, which regulates medical laboratories under the Clinical Laboratory Improvement Amendments, or CLIA, has balked at creating special oversight for genetic tests. At a minimum, people ordering genetic tests should ask if the laboratory is certified under CLIA. "I would also look for a lab that's participating in the College of American Pathologists or ACMG proficiency testing," says ACMG's Watson. Four of the testing companies we used, DNA Direct, HealthCheckUSA, Kimball Genetics, and NeuroMark, use CLIA-certified labs. CyGene plans to apply for CLIA certification this month, Munzer says.

We sent CyGene a sample of DNA from Tate the dog. The results reported that Tate had a "moderately elevated risk of macular degeneration." Geneticists say dog DNA is similar enough to human DNA to return a result. But dogs don't get macular degeneration.

A 2006 Government Accountability Office study found that nutrigenetic tests, which offer nutritional advice to reduce disease risk—based on your DNA—failed to do so. "Clearly consumers are being misled by this modern-day snake oil," Sen. Gordon Smith, a Republican from Oregon and chairman of the Special Committee on Aging, says of the nutrigenetic tests. Smith and Massachusetts Democratic Sen. Edward Kennedy plan to introduce legislation aimed at imposing tighter controls on all genetic tests.

Patient privacy. Despite the paucity of oversight, some clients say the tests are quite literally just what the doctor ordered. After Susan Smith, 37, of North Carolina had a stillbirth and a miscarriage, her doctor suggested that she take a

test for Factor V Leiden, a hereditary disorder that boosts the risk of blood clots. But he proposed that she order the test through DNA Direct so that the results wouldn't be part of her medical record. Smith tested positive. "No one wants to have bad news," she says, "but I felt somewhat liberated by knowing it."

Almost all states have laws offering some protection against genetic discrimination by medical insurers. Federal legislation prohibiting genetic discrimination in employment or insurance has failed to pass Congress. "We get two or three calls a month from people who have lost their jobs or lost their insurance," says Sharon Terry, president and CEO of the Genetic Alliance, a consumer advocacy group.

The DTC genetic testing firms aren't required to protect patient privacy under federal law, as hospital and healthcare facilities must. And there is no guarantee that the firms won't sell or share medical results with insurers or another company. The privacy question cuts another way. A person who hides test results could also miss out on important healthcare—say, more careful reading of mammograms for someone who's BRCA-positive. "It makes for an incomplete medical record that will not be transportable," says Wiesner. "I would submit that that's not modern medicine."

For most people, the odds of having a hereditary disorder are so small that testing doesn't make sense. Elissa Levin, a genetic counselor and clinical director of DNA Direct, says that 40 percent of their clients test positive, a much higher number than would be found in the general population. "The vast majority of people who are testing are testing due to personal diagnosis, family history, or 1 in 5 have a known family mutation," she says. "It's not the worried well."

DNA Direct's most popular test is its \$199 screening for hemochromatosis, which elevates iron in the blood and can lead to liver cancer. Ever since a gene that causes the disease was detected in 1996, doctors have debated widespread screening. Sandra Thomas, president of the American Hemochromatosis Society, encourages people who contact her to use DTC tests and thinks that everyone should be screened for the disease, which killed her mother. But a National Institutes of Health study of almost 100,000 people in 2005 found the correlation between gene and disease not strong enough to be useful as a screening tool. The U.S. News staffer, who took the test through HealthCheckUSA, had no family history and came up negative. "Some people have cirrhosis and liver cancer, and some people have the same genetic profile and don't even have iron overload," says Paul Adams, a gastroenterologist at the University of Western Ontario who led the NIH study.

Genetics is notoriously confusing, and most people need help interpreting test results. Most primary care doctors never studied genetics in medical school, and

there are only about 800 U.S. physicians board-certified in genetics. About 3,000 genetic counselors have master's degrees, but they aren't doctors and thus can't give medical advice.

Annette Taylor, president of Kimball Genetics, is both a geneticist and a certified genetic counselor, and she believes that counseling and interpretation are essential for both patients and doctors. She requires customers to give a healthcare provider's name and faxes them the results. Our celiac disease tester, a 38-year-old male who has irritable bowel syndrome, called the counselors at Kimball because he couldn't decipher the written results. "A DQA 1*05 allele (*0501 or *0505) was detected but neither of the DQB1*02 alleles (*0201 or *0202) was detected," they read in part. The counselor, who said she had a master's in genetic counseling, spent 20 minutes talking with him by phone. He said she explained that the test didn't rule out celiac, which is caused by an autoimmune reaction to gluten in food, but it didn't definitively diagnose celiac, either. A third of the population had this genetic pattern, she said, but only about 1 percent has celiac. She suggested the tester talk with his doctor about a blood test that would detect gluten antibodies. She also suggested, twice, that he buy the test from Kimball, raising the question of whether her focus was on interpreting tests or selling them. "She was just making it convenient for him," says Taylor. "We would never say anything that is not medically indicated."

To gauge how phone counseling compared with face-to-face guidance, U.S. News asked Deborah Nagler of Teaneck, N.J., to call DNA Direct. Nagler had a double mastectomy in 2002 at age 50, after learning she had a BRCA mutation (her sister, mother, and aunt died of breast cancer). The DNA Direct counselor called her at home after she filled out an online form. "I found her to be very empathetic, very knowledgeable, and that there was relative parity with the face-to-face experience I had," says Nagler. "The counseling piece is really, truly critical. It's a personal and emotional upheaval to receive the news."

Nagler worries about her two daughters, both in their 20s. "I could be delivering death sentences to my children, and to my children's children." With more access to genetic testing, more families will face these struggles. The hope is that they will do so armed with real medical insight, not hype.

A BRAVE NEW WORLD

Some genetic tests are already in wide use. Others have yet to fulfill their promise. Tests include:

Carrier screening. Pregnant women can be tested for mutations they can pass on to their children.

Prenatal screening. Tests that pull a fetus's genes from amniotic fluid or chorionic villi can detect disorders.

Newborn screening. All babies are tested right after birth for treatable diseases.

Forensic. DNA can identify criminal suspects or victims, as well as establish paternity.

Predictive. A few tests can help gauge the odds of having a familial version of a disease.

Diagnostic. Genes can reveal or confirm inherited diseases such as sickle cell, as well as rare disorders.

Nutrigenomic or nutrigenetic. Sold as offering customized nutritional advice, but they're questionable.

Pharmacogenetic. Doctors now use genes to tailor cancer treatments to the individual patient. More are in the works.

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