Risky Business

Now, anyone with a thousand dollars can discover the secrets lurking in their DNA.

But are we ready for mail-order genetic tests?

BY JAMIE TALAN

hen scientists discovered in 1993 that the gene known as apoE4 was a risk factor for Alzheimer's disease, Janet Walsh was at the front of the line to get a DNA test. Her concern was this: Her father developed Alzheimer's when he was 58. Plus, there was Alzheimer's disease in her mother's family.

Walsh wanted to know whether that gene could unravel the medical mystery that left her beloved father demented and talking to trees. Having a copy of the apoE4 gene didn't guarantee that she would develop late-onset Alzheimer's. But it did

increase the odds by three to four times compared to those with another form of the apoE gene, which is handed down in three different varieties: E2, E3, and E4. Having two copies of the E4 gene, one from mom and one from dad, increases the odds even more, around seven-fold.

An Alzheimer's scientist agreed to scan Walsh's genome—that is, all of her genetic information—to see which type of apoE gene she inherited. She was E4/E4, the worst possible roll of the apoE dice. In spite of the fact that there are no effec-

tive treatments to stop the progression of Alzheimer's, Walsh does not regret having the test done. She has used the results to stay on top of her cognitive game through nutrition, exercise, and mental stimulation. But many doctors and patients are concerned that the genetic testing industry is moving too quickly in offering tests directly to consumers.

READY, SET, GENOME!

Now, anyone with a thousand dollars can discover the secrets lurking in their DNA, thanks to companies springing up that offer sequencing of the human genome. Provide a sample of spit and they'll read out your genetic Book of Life. These companies promise to tell you what hundreds of thousands of genetic markers mean to your individual health. Some will even link genes to a slew of traits such as height.

"I'm not sure anyone was prepared for the speed of this," says Francis Collins, M.D., Ph.D., former director of the National Human Genome Research Institute. Dr. Collins, who stepped down as director in August 2008, led the federal effort to sequence the human genome. Since the result of this global scientific project went public in 2003, scientists have

> developed technology allowing them to find risk genes for a wide range of conditions. A growing number of companies are combing the scientific literature so that they can test for more risk genes.

> At the same time, doctors and patients are coming together to discuss the implications of these mail-order genetic tests. In July 2008, Dr. Collins led a panel on direct-to-consumer testing at a meeting held by the Genetic Alliance, an organization dedicated to improving the lives of people with genetic disorders. Two

months earlier, he led a similar panel discussion at the first World Science Festival, held in New York City.

"I'm worried that we are developing applications before we know enough about genes that confer modest risks," Dr. Collins says. A modest risk could mean that someone is two to three times at greater risk, which is small if the disease only shows up in one percent of the population.

According to Janet Walsh, the information needs to be interpreted for patients. "You have to be able to say what we can fix, what we can change, and what we can squeeze by on," she says. Walsh exercises, eats healthy foods, and keeps herself MICROZOA LIMITED/GETTY IMAGES

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mentally fit by reading and exposing herself to novel experiences. She is also part of a study that scans her brain and tests her mental acuity every 18 months. There are no signs that Alzheimer's will be knocking on her door anytime soon, if ever. But once in a while she'll read something about the apoE4 risk for Alzheimer's that throws her a curve. She recently read a story in *Time* magazine describing people with her genetic makeup as "going off a cliff at 60." She is 52.

DNA ON DEMAND

These companies, which have enticing names—23andMe, DeCodeMe, Navigenics—offer sequencing with the latest technology. (The name 23andMe is based on the fact that human beings have 23 pairs of chromosomes).

Computer programs interpret the genetic data. Then, the customer is given a read-out of their possible risks for diabetes, multiple sclerosis (MS), obesity, male-pattern baldness, infertility, heart disease—the list goes on. Some of the companies will also connect the genetic dots for traits such as musical ability and athletic prowess.

"There is a segment of the population that wants to be proactive and understand their risks for disease," says Dietrich Stephan, Ph.D., founder of Navigenics. "They are ready."

Dr. Stephan created Navigenics in 2006. He was working for a company called TGen that uses genetic technology to scan for single nucleotide polymorphisms, or SNPs, which are single changes at any point in a person's genetic code. (See "What Do Genetic Tests Look For?" box.) Navigenics is staffed by doctors, geneticists, engineers, and ethicists who offer state-of-the-art genetic testing to anyone willing to pay for it. For a thousand dollars, customers sign on to receive a spit kit in the mail. They send it back for analysis of 500,000 genetic markers—the single nucleotide polymorphisms.

According to Dr. Stephan, the idea behind Navigenics is to be the "interpretive engine" for someone's genome sequence. In other words, Dr. Stephan says, the company "ranks disease predisposition so you can work with your physician to stay healthier longer." Navigenics analyzes genetic information for 30 different common diseases. When Dr. Stephan put his own DNA into the machine, a few risk genes popped out: for obesity and prostate cancer.

"When someone knows they are at higher risk for a condition, there are things that they may be able to do to lower that risk," says Dr. Stephan, who watches his weight and undergoes routine screening for prostate cancer.

But what about finding out that you are at high risk for a disease that can not be prevented or effectively treated? What about finding out you're at high risk for Alzheimer's? Stephan's company offers information on the apoE genotype, asserting



What Do Genetic Tests Look For?

The most common genetic analysis is called a whole genome association study. With a sample of DNA, machines are able to search for differences across the genome among large numbers of individuals. Even though people look and act so differently, only 0.1 percent of the human genome varies from person to person. Scientists seek out what are called "single nucleotide polymorphisms," or SNPs, in the genome. SNPs are single changes at any one point in the genetic code. At least 10 million SNPs have been identified, and machines are now able to analyze a person's DNA for up to a million of them. In whole genome association studies, scientists look for SNPs in a person's genome that occur more frequently in connection with specific diseases.

that individuals have a right to know. Geneticists at Navigenics recently identified an E4/E4 carrier, and a genetic counselor called to talk to him about the results.

"After the counseling, he did not seem distressed. He was eager to understand the genetic information," Dr. Stephan says.

MORE THAN DISEASE RISK

But while he believes in delivering results on an increased risk for dementia, Dr. Stephan stops short of providing information that some of his competitors offer. 23andMe and DeCodeMe both offer genetic data on traits like athletic ability or height. Dr. Stephan believes that this kind of service creates "an ethically slippery slope. There are major societal ramifications. People can use this information to select a mate genetically loaded for height. It's not appropriate."

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Joanna Mountain, senior director of research for 23andMe, says that many of the people who have signed on are simply "curious and want to be a part of the growing research." The California-based company, a five-minute drive from Navigenics, currently offers information on genes that may increase one's chance of inheriting 90 different diseases and traits. It is Mountain's job to ascertain what 23andMe can pull out of someone's genome that might be of value. They also offer computer analysis of a person's ancestral history based on genetic testing of the Y-chromosome and maternal mitochondrial DNA.

Doctors are also finding that genes can help predict how individuals will respond to different medications. This may come in handy when choosing among drug options. Patients whose genes make their body unable to properly metabolize one medication could be put on a different one instead. Called pharmacogenetics, this new field may lead to tailored treatments based on an individual's genetic make-up.

"We acknowledge that we are in the early days of our understanding of the associations between our traits and our genome," Mountain says. 23andMe customers must sign a consent form that states their information can be used for research (without their names or any other identifying information).

Customers are also continually asked to participate in questionnaires about lifestyles and health histories. "We want to tease out the relationship between genes and how they interact with the environment," Mountain says.

23andMe is collaborating with researchers at universities to use the mounting genomic information in a variety of studies. "Our service is aimed at people who are comfortable with a broad analysis of their data," Mountain says.

THE PROBLEM OF INTERPRETATION

But many of these people are less interested in contributing to research than getting a snapshot of the genes that make them who they are. Misha Angrist, 44, decided to have his genome analyzed as part of his research for a book on "personal genomics." Angrist enrolled in Harvard geneticist George Church's Personal Genome Project (PGP), a research experiment that would read out, analyze, and interpret anonymous genetic markers as well as the protein-coding part of his genome. Before his PGP consult in October, Angrist sent his marker data to Mike Cariaso, who runs the community genetic interpretation Web site **SNPedia.com**. Cariaso's analysis suggested that compared to the population at large, Angrist had genetic variants (or "alleles") that were associated with a higher risk for MS and rheumatoid arthritis. But when he then sent his spit sample to Navigenics, the risk for MS all but disappeared. What is becoming clear is that these companies may use similar technology to sequence a person's genome, but there are vast differences in the way specific genetic information is interpreted. Boonsri Dickinson, 26, is a science journalist at *Discover* who decided to get tested for a cover story she was writing for the magazine. 23andMe, DeCodeMe, and Navigenics each sent her spit kits. She took her saliva samples and sent them back.

"You get different results from each company because they calculate risk differently," Dickinson explains. Her genetic story was particularly difficult to interpret because she is half Asian and half Caucasian. These companies use population data to calculate a person's risk for various diseases, and the data are generally culled from studies conducted on Caucasians with European ancestry.

The companies delivered information on about 80 different conditions, with Navigenics handing down her apoE genotype. Like most of the population, she does not carry an E4 variant. Her risk for age-related macular degeneration was three times that of the general population according to the two companies that tested for it. But while DeCodeMe and Navigenics said that she was at high risk for Crohn's disease, an autoimmune condition, 23andMe disagreed.

THE RESULTS ARE IN-NOW WHAT?

Whole-genome association studies are not diagnostic. In other words, identifying SNPs and linking them to a greater risk for a specific disease does not mean that the person has the disease or will ever get it. Individuals buying such testing should know that the data are limited and interpretation is subjective and often confusing.

But if you are interested in plunking down money to read your biological biography, consider how you would use the information, cautions W. Andrew Faucett, M.S., a certified genetic counselor and director of the Genomics and Public Health program at Emory University School of Medicine in Atlanta, GA. "We all know we need to make lifestyle changes," he says. "Would this information help them? If they found out that they had some risk, would they be terrified?"

Furthermore, "we are talking about modest risks," according to Dr. Collins. He doesn't believe that enough is known about genetic risks to use genetic information for prevention. For instance, he says, scientists have identified 16 or 17 risk genes for diabetes, but these may only comprise 10 percent of the genes that put people at risk for the disease. Scientists have much to learn about the human genome, including how one genetic variant works with other genetic variants to confer risk, which genes protect against certain diseases, and how genetic information interacts with one's environment and life experiences. "There is a big gap in information," says Dr. Collins, who thinks it will take a lot more work to determine how

these environmental and lifestyle factors—everything from stress and diet to air pollution—affect the risk for disease.

James P. Evans, M.D., agrees. In May 2008, the University of North Carolina geneticist joined the stage with Dr. Collins, British sociologist Nikolas Rose, Misha Angrist, and Paul Nurse, M.D., of Rockefeller University in New York City. They discussed the issue of direct-to-consumer genetic testing at the world science festival. "We all have genetic problems that will come to roost at some point" in our lives, Dr. Evans says.

What's more, no one knows enough about the impact of these risk genes on human health. What if someone has a low risk for heart disease but smokes and struggles with obesity and high cholesterol? Do these lifestyle factors cancel out a person's genetic legacy? "We just don't know," Emory's Faucett says.

But this is exactly why Dr. Stephan of Navigenics believes that people should know their genetic risks, so they can make whatever changes are possible. "Over time, this will be something routine that physicians will do with their patients early on so they can get them on a personalized routine toward good health." An example of this early identification arrives on the heels of new studies that identified a gene putting people at risk for melanoma, a deadly skin cancer. "What if we could tell someone that they carry these genes so that they limit their exposure to sun? Melanoma is easy to prevent," Dr. Stephan says.

BUYER BEWARE

The growth of genetic information could make the one-sizefits-all medical approach obsolete. "Genetics will make us realize that we need targeted messages," says Dr. Collins, who is writing a book on personalized medicine. The technology is advancing so rapidly that genetic information doubles every 18 months, he says, adding, "What we know about hereditary factors is just scratching the surface. Most of the hereditary factors have not been discovered. As they are discovered, the ability to make predictions about risk will get stronger. The environment is a critical part of these conditions. I think there will reach a point where lots of people will be interested in having the information, and there will be a point where we will have validated interventions that people can take advantage of to reduce their risk."

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Still, there are people who worry about the strength of the associations, and state officials who worry that the companies are unregulated and may be taking advantage of the public interest in genomics. Earlier this year, the state of California sent out "cease and desist" letters to

dozens of companies throughout the country offering online genetic tests direct to consumers. While state health officials wanted companies to stop providing services to people in the states they represent, it is not clear that these companies are doing anything illegal. The "cease and desist" letters stated that California public health code requires licensing of clinical laboratories that test biological specimens in California, and that laboratories can't conduct genetic testing for individuals without a prescription from a doctor. Joanna Mountain of 23andMe, whose company was on the list, says that her company resolved the issue with the California Department of Public Health. In August, they issued the company a license allowing them to continue to operate in California.

The government is studying the issue of direct-to-consumer genetic testing in an attempt to develop standards for the field. Right now, the Food and Drug Administration has oversight on the testing itself, and mandates that companies doing these tests use a certified laboratory. But there is no one regulating the interpretation of the tests, or whether the analysis comes with assistance from a genetic counselor. Consumers have to be careful.

"There is a lot of snake oil on the Web," Dr. Collins says. "I'm torn about this development. On the one hand, it is exciting to see the public embracing these clinically validated discoveries. On the other hand, we don't have the data to know what interventions will be successful for people at risk." Plus, he says, "The risk factors are pretty small. There is a danger that people will be turned off when they realize that the information is not helping as much as they thought."

Janet Walsh, for one, is glad that she knows her genotype. But she feels that people don't need genetic sequencing to know whether they are at risk for many diseases. "Just look at your family tree," she says. "If you have a close family member with Alzheimer's, you are probably at increased risk. I felt I had to find out. But for some people it would be devastating to know."

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