

Peering Into the Future: Genetic Testing

Genetic testing is transforming medicine—and the way families think about their health. As science unlocks the intricate secrets of DNA, we face difficult choices and new challenges.

By Claudia Kalb

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Dec. 11, 2006 issue - The year is 1895 and Pauline Gross, a young seamstress, is scared. Gross knows nothing about the double helix or the human-genome project—such medical triumphs are far in the future. But she does know about a nasty disease called cancer, and it's running through her family. "I'm healthy now," she reportedly confides to Dr. Aldred Warthin, a pathologist at the University of Michigan, "but I fully expect to die an early death."

At the time, Gross's prediction (she did indeed die young of cancer) was based solely on observation: family members had succumbed to colon and endometrial cancer; she would, too. Today, more than 100 years later, Gross's relatives have a much more clinical option: genetic testing. With a simple blood test, they can peer into their own DNA, learning—while still perfectly healthy—whether they carry a hereditary gene mutation that has dogged their family for decades and puts them at serious risk. Ami McKay, 38, whose great-grandmother Tilly was Gross's sister, decided she wanted to know for her children's sake. In 2002, the answer came back: positive. "It changes who you are," says McKay.

Genetic testing is changing medicine, too. Three years after scientists announced they had sequenced the human genome, new knowledge about how our genes affect our health is transforming the way diseases are understood, diagnosed, treated—and even predicted. Today gene tests are available for more than 1,300 diseases, including cystic fibrosis and hemophilia. And now, as genetic screening gets cheaper and faster, researchers are hunting down the biological underpinnings of more-complex disorders that involve multiple genes—big, rampaging illnesses that strike millions of Americans every year. On the list: type 2 diabetes, Alzheimer's, heart disease and depression. If the scientists are right, genetic tests for some of these diseases could be available by 2010. Testing positive doesn't guarantee that you'll get the illness, but it does help determine your risk. "We are on the leading edge of a genuine revolution," says Dr. Francis Collins, head of the National Human Genome Research Institute.

Genetic testing today starts at the earliest stages of life. Couples planning to have children can be screened prior to conception to see if they are carriers of genetic diseases; prenatal tests are offered during pregnancy, and states now screen newborns for as many as 29 conditions, the majority of them genetic disorders. For Jana and Tom Monaco, of Woodbridge, Va., early testing has made an enormous difference in the lives of their children. Their journey began in 2001, when their seemingly healthy third child, 3 1/2-year-old Stephen, developed a life-threatening stomach virus that led to severe brain damage. His diagnosis: a rare but treatable disease called isovaleric acidemia (IVA), marked by the body's inability to metabolize an amino acid found in dietary protein. Unknowingly, Jana and her husband were carriers of the disease, and at the time, IVA was not included in newborn screening. The Monacos had no warning whatsoever.

Not so when Jana got pregnant again. Her daughter, Caroline, was tested by amnio while still in the womb. Knowing Caroline had the mutation, doctors were able to administer medication the day she was born. And the Monacos were prepared to monitor her diet immediately to keep her healthy. Today Stephen, 9, is unable to walk, talk or feed himself. Caroline, meanwhile, is an active, healthy 4-year-old. Genetic testing, says Jana, "gives Caroline the future that Stephen didn't get to have."

The future is what drives many adults to the clinic. The gene tests currently offered for certain diseases, like breast and colon cancer, affect only a small percentage of total cases. Inherited mutations, including BRCA1 and 2, contribute to just 5 to 10 percent of all breast cancers, and the main gene variants involved in colon cancer

account for 3 to 5 percent of diagnoses. But the impact on a single life can be huge. The key: being able to do something to ward off disease. "Genetic testing offers us profound insight," says Dr. Stephen Gruber, of the University of Michigan. "But it has to be balanced with our ability to care for these patients."

Ami McKay now has an annual colonoscopy. Another kind of genetically driven colon cancer, familial polyposis, is treated by removing the colon. The risk of breast and ovarian cancers in people with BRCA mutations can be reduced by frequent screening and radical surgery, too. Having healthy breasts or ovaries removed isn't easy, but the payoff—an end to constant anxiety and a pre-emptive strike at disease—can be well worth it. "Most women I've met who've had prophylactic surgery are glad they made the choice even if they're unhappy they were put in that position," says Sue Friedman, a breast-cancer survivor and head of FORCE, an advocacy and support group focused on hereditary cancers. "It's a double-edged sword."

Genetic testing, exciting as it may seem, isn't always the answer. When Wendy Uhlmann, a genetic counselor at the University of Michigan, teaches medical students, she flashes two slides on a screen side by side. One says ignorance is bliss. The other: knowledge is power. That's because the value of testing becomes especially murky—and ethically complicated—when there is no way to prevent or treat disease, as in the case of early-onset Alzheimer's, which often strikes before the age of 50, or Huntington's.

Today only about 5 percent of people who are at risk for Huntington's—which is caused by a single gene and leads to a progressive loss of physical control and mental acuity—take the test. Many are worried that genetic testing will put their health insurance or job security in jeopardy. While there have been few documented cases of discrimination, nobody can say for sure what will happen as more disease genes are discovered and more Americans sign on for predictive testing. States have a patchwork of regulations in place, but what needs to happen now, experts say, is for Congress to pass the Genetic Information Nondiscrimination Act, which would put a federal stamp of approval on keeping genetic information safe.

For Shana Martin, 26, of Madison, Wis., the decision not to get tested is far more personal. Shana grew up watching her mother, Deborah, battle Huntington's. Now a fitness instructor (and the current world champion in logrolling, no less), Shana is young, strong, healthy—and not interested in opening her genetic Pandora's box. "I don't know how well I'd handle a positive result, and with how happy I am right now, that would just put a real shadow over my life," she says. "I'm much more comfortable with it being an unknown."

Some people, however, can't live with uncertainty. Uhlmann's patient Stephanie Vogt knew Huntington's ran in her family—her paternal grandfather and his three brothers all died of complications of the disease—and she wanted to find out where she stood. "As soon as I found out there was a test, I just had to do it," she says. In August 2000, after comprehensive genetic counseling, Stephanie, her sister, Victoria, and their mother, Gayle Smith, learned her results: positive. "It was like a scene out of 'The Matrix,' where everything freezes and starts again," says Stephanie, now 35 and single. Victoria, 36, who has since tested negative, says she hopes to care for her sister down the road. She also prays for a cure. Knowing isn't always easy. On good days Stephanie feels empowered; on bad days she's frightened. "But most of the time," she says, "I'm comfortable with the fact that I have the knowledge."

It's not just their own health that people care about. There is also the desire to prune disease from the family tree. Today, using a scientific advance called preimplantation genetic diagnosis (PGD), couples can create embryos through standard fertility methods, then screen them for genetic disorders, selecting only those that are mutation-free for implantation. The practice is expensive (in the tens of thousands of dollars) and not widespread, but a recent survey of fertility clinics by the Genetics and Public Policy Center found that 28 percent have used PGD to help couples avoid diseases that strike in adulthood, like breast cancer and Huntington's. Kari and Tim Baker knew they had to give it a try. Kari's grandfather died of Huntington's, and her mother was diagnosed in 1999. Kari, a board member of the Huntington's Disease Society of America, wanted to spare her kids. Twins Brooklyn and Levi are now vibrant 2½-year-olds who will never have to worry. "There's great joy and peace in knowing we did everything we could to not pass this on," says Tim.

Testing is just one piece of the genomic revolution. A major goal is to create new sophisticated therapies that home in on a disease's biological glitch, then fix the problem. Already, genes are helping to predict a patient's response to existing medications. A prime example in this field of pharmacogenetics, says Dr. Wylie Burke of the University of Washington, is a variant of a gene called TPMT, which can lead to life-threatening reactions to certain doses of chemotherapy. A genetic test can guide safe and appropriate treatment. Two genes have been identified that influence a person's response to the anti-blood-clotting drug warfarin. And scientists are uncovering genetic differences in the way people respond to other widely used medications, like antidepressants.

Knowing a patient's genotype, or genetic profile, may also help researchers uncover new preventive therapies for intractable diseases. At Johns Hopkins University School of Medicine, Dr. Christopher Ross has tested several compounds shown to slow the progression of Huntington's in mice. Now he wants to test them in people who are positive for the Huntington's mutation but have not developed symptoms—a novel approach to clinical drug trials, which almost always involve sick people seeking cures. "We're using genetics to move from treating the disease after it happens," he says, "to preventing the worst symptoms of the disease before it happens."

Early on, the targets of genetic medicine were rare, single-gene disorders, like sickle-cell anemia and Tay-Sachs. Now it's time for the big guns—genetically complex but common conditions like heart disease. A number of genes have already been linked to such illnesses, but many more are at work. The human-genome project, which defines the 99.9 percent of DNA we all have in common, was the starting point. Act II: the "Hap Map"—a genetic atlas completed last year that zeroes in on the .1 percent of DNA that differs among individuals. The Hap Map is proving to be a boon to scientists, allowing them to scan whole chunks of DNA, rather than single genes, to isolate mutations responsible for disease. Already, the Hap Map has helped scientists uncover several gene variations that contribute to macular degeneration, the leading cause of vision loss in older people. At Harvard, Dr. Rudolph Tanzi is using the Hap Map to track down gene mutations that cause the common, late-onset form of Alzheimer's, which could strike as many as 16 million Americans by the year 2050. Tanzi's work is funded by the Cure Alzheimer's Fund, a nonprofit that is investing \$3 million to unravel the Alzheimer's genome, which it hopes to complete by the summer of 2008. Tanzi says a prototype genetic chip to test for the disease could be available within five years. Dr. Eric Topol, of Case Western Reserve University, is hunting down genes that predispose people to heart attacks.

Private companies, interested in developing drug therapies, are investing in DNA as well. In Iceland, deCode Genetics has pinpointed a gene mutation for type 2 diabetes called TCF7L2. One copy of the mutation increases an individual's risk by 40 percent, two copies by 140 percent, says CEO Kari Stefansson. Stefansson says he expects a genetic test will be available as early as next year. And a joint effort by NIH and Pfizer, announced earlier this year, is searching for genes for a host of diseases, including schizophrenia, bipolar disease and severe depression.

As science advances, business follows. Today genetic testing usually takes place in specialized clinics, where patients undergo thorough counseling both before and after testing so that they—and other family members—understand the emotional and practical implications that might arise. But do-it-yourself online testing companies, advertised directly to consumers, are springing up on the Internet. Ryan Phelan, CEO of DNA Direct, founded in 2004, says her site provides a "virtual genetics clinic," making testing as easy as sending in a cheek swab. (Cost: anywhere from \$200 to \$3,300.) DNA Direct provides counseling and does not sell remedies after results are in. But other companies are not so scrupulous, marketing tests that have little to no scientific validity, then pushing products as therapy. Critics say they need more oversight. "What you have here," says Dr. Adam Wolfberg, of Tufts-New England Medical Center, "is a real blurring of the lines between medical testing and product marketing."

Scientific revolutions must be tempered by reality. Genes aren't the only factors involved in complex diseases—lifestyle and environmental influences, such as diet or smoking, are too. And predictions about new tests and treatments may not come to pass as fast as researchers hope—they may not come at all. Still, it's hard not to get excited about the future, especially when you consider the medical competition now underway: NIH has challenged

researchers to come up with a method, within the next 10 years, to sequence a single human genome for \$1,000 (today's cost: \$5 million to \$10 million). Assuming it works, one day not too far in the future, each of us will go to the doc, hand over our blood and get back our personalized biological blueprints. "It's an astounding curve to be riding," says Collins. Hold on to your DNA.

With Anne Underwood and Jonathan Mummolo

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