

GENE TESTS: BEHIND THE HYPE

By John Carey
Photograph
by Stephen Voss

The science of decoding DNA has become a business, but can it accurately tell you what diseases you're at risk for? The claims are extravagant—and, say scientists, way overblown

If Greg Lennon is right, then the personal genome gold rush has a major flaw: There's not much gold there—not yet.

In the past year, companies have launched high-profile efforts to read the future in people's genes. For \$399, a Google-backed startup called 23andMe collects saliva samples from its customers, looks at nearly 600,000 genetic variations in their DNA, and describes what these reveal about the donor's traits, ancestry, health, and risk of diseases. Another company in the headlines, Navigenics, not only extracts information from 1.8 million variations, or "markers," in a tissue sample, but also taps the expertise of genetic counselors and scientists at Harvard and other institutions. The price: \$2,500, plus a \$250 annual fee to get customized bulletins on the latest discoveries. "The technology lets you know who is at risk for Alzheimer's, diabetes, cancer, and other diseases," says Navigenics Chief Executive Officer Mari Baker.

Not so fast, says Lennon, a PhD geneticist and entrepreneur. Contrary to the hype about genetic testing, this first wave of direct-to-consumer ventures is likely to be a bust,

he believes. The slim, soft-spoken Lennon, 51, is in a good position to know. He's a veteran of both the government's Human Genome Project and biotech startups, and he has ridden the roller coaster of hype and failure. He predicts that the payoff from the explosion in knowledge about human genes—and from the business model espoused by 23andMe and its ilk—won't come for 10 years. Right now, the personal gene-testing companies glean medical insights from individual bits of DNA, rather than from whole genes. So far that may be no better than what is learned the old way, from family histories: "Most people can save themselves \$1,000 just by asking Aunt Clara what runs in the family," says Lennon.

"PARLOR GAME"

Such skepticism is surprisingly common among scientists. "I see personal genomics as a kind of recreational parlor game rather than a useful endeavor," says Dr. James P. Evans, professor of genetics and medicine at the University of North Carolina, Chapel Hill. "There's a potential for



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harm in false reassurance and false anxiety, but mostly it's a waste of money."

Of course, even parlor games can make money. And in the long run, Lennon, Evans, and others think that reading people's DNA will prove to be a tremendous medical boon. Lennon himself is a believer and continues to place bets on the field: His latest venture, called SNPedia, is a repository for all the data streaming from around the world linking genetic variations to health and disease. Launched in 2006 by Lennon and a computer-whiz buddy, it's a Web site supported by ads and licenses, which anyone can browse for free.

But Lennon and many academics contend that the claims of the new gene-testing startups are premature and overblown. 23andMe, which is also backed by biotech powerhouse Genentech and was co-founded by Anne Wojcicki, wife of Google's Sergey Brin, promises on its Web site to "help you understand how your genetics influences more than 80 diseases, health-related conditions, and traits." Another gene-testing company, deCODE Genetics, also makes some grand claims on its deCODEme Web site: "You'll find out where your ancestors came from" and "make more informed decisions about your health." Yet the information we can extract from common DNA variations falls far short of a predictive blueprint for future health. It provides only small statistical links to illness, along with imperfect hints at a customer's origins.

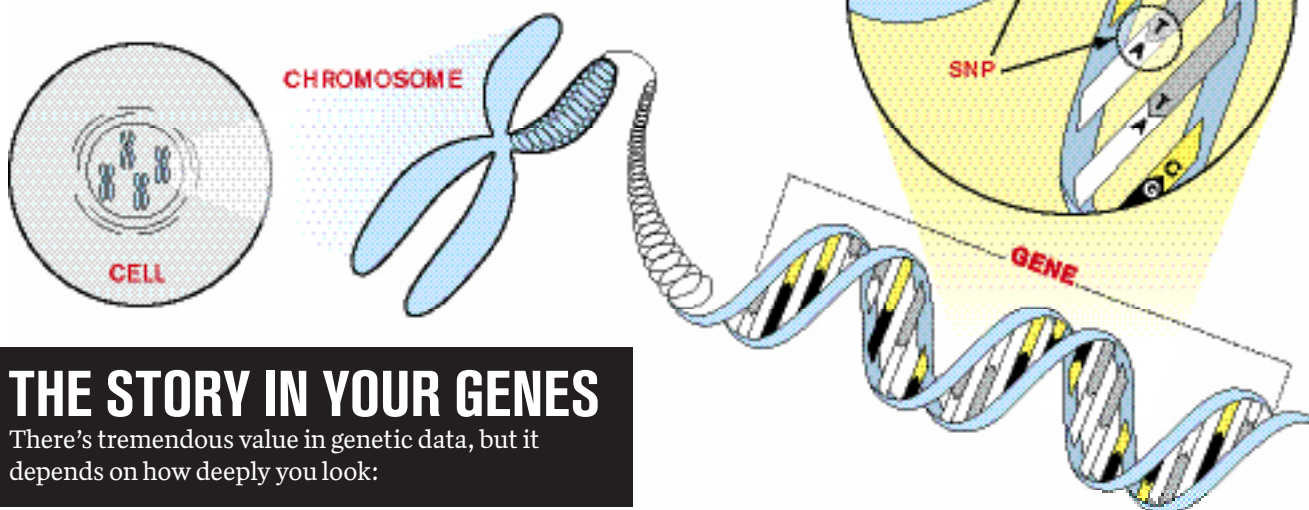
This reality struck Lennon when he had his own DNA tested several years ago with the same basic technology now marketed by 23andMe, then analyzed it using his SNPedia database. Getting the results seemed exciting at first, he says. He

was intrigued to learn he has genetic markers linked with an increased risk of heart disease and decreased risk for certain cancers. But then he thought, so what? Not only were the purported changes in risks too small to mean much, he wasn't sure he believed them. "I hit the phase of realizing, 'Boy, how little we know today,'" he says.

The real message in Lennon's genes? "To me, what it came down to was just, don't smoke, eat better, and exercise more," he says. As for the other big selling point of personal genetic analysis, revealing ancestry, he tells a story about his mother. She signed up for a genealogy test offered by National Geographic, Lennon says, "but it was a \$100 letdown." The test said she had European origins. No surprise: "She was born in Germany to German parents. The amount of new information was pitiful."

LOOKING UNDER THE LAMP POST

The industry will have to do a lot better than this—and it will, say scientists. But first, gene sequencing technology must advance to the point where researchers can examine and compare the entire genetic codes of tens of thousands of people.



THE STORY IN YOUR GENES

There's tremendous value in genetic data, but it depends on how deeply you look:

1 Each person's genome consists of 3 billion pairs of **DNA** molecules twined into the long double helix that forms our 46 **chromosomes**. Those paired bits of DNA come in four types, represented by A, C, T, and G, which form our **genes**.

2 Most of the billions of letters are the same in every person. But they differ at perhaps 10 million places. You might have a "T" at one location, while someone else has a "C." These differences are called **SNPs**, for single nucleotide polymorphisms.

3 Mutations in genes cause certain diseases, such as cystic fibrosis and sickle cell anemia. In contrast, SNPs usually are only weakly linked to the risk of diseases, studies show. And so far, the personal genomics companies analyze only SNPs.

4 Among other problems, today's gene testing covers only a small fraction of SNPs. But even if all SNPs were tested, is it really medically useful to know that your SNPs are associated with, say, a 5% higher risk of multiple sclerosis?



Inflated expectations:
At a September “spit party” hosted by 23andMe, invitees supply samples for free genetic testing

And they must be able to analyze genetic data in light of each individual’s entire medical history, including lifestyle choices and environmental exposures.

Consider the case of Mike Spear, communications director for Genome Alberta, a Canadian nonprofit. He recently got his genes read by 23andMe. “One of the things that stood out was that I should have male pattern baldness,” he says. Not so. In his fifties, Spear has a full head of thick, wavy hair.

Dr. Robert C. Green, professor of neurology and epidemiology at Boston University, had a similar experience last year. Both Navigenics and 23andMe probed his genes for free. They found that his variations put him at no more than average risk for heart disease. That fits with what a casual observer might think of Green, who is trim and fit, a marathon runner with no family history of heart problems. But two years ago, when running, he felt chest pain that landed him in the hospital, where doctors diagnosed severe disease in three arteries and performed a bypass operation. Given Green’s healthy lifestyle, “my risk has to be genetic,” he says. “Yet where the tests could have alerted me to the problem genes, they did not.”

Green wasn’t entirely surprised. “This is an exciting industry,” he says, “but the current information has little or no medical value.” The reason: basic biology. The human genetic code, or genome, consists of about 3 billion pairs of chemicals that make up DNA (table). The vast majority of “base pairs” along the chain—about 99.7%—are identical in all individuals. But an estimated 10 million of them show variations. These differences are called single nucleotide polymorphisms, or SNPs—hence the name of Lennon’s venture, SNPedia. SNPs (pronounced “snips”) help explain why we all look different, and several thousand have been statistically linked with diseases. That’s the basis for claims by 23andMe, deCODE, and Navigenics that they can pinpoint your risk of heart disease or baldness.

The problem is, these links are often dubious or less informative than they may first seem. Just because a study finds a correlation between a SNP and a disease “doesn’t mean that new science won’t invalidate it,” cautions Dr. David J. Brailer, a former top health technologist in the Bush Administration.



Brailer is now chairman of Health Evolution Partners, an investment firm that backs health-care startups, but personal genomics companies are “not what we do,” he says.

Why are the links between SNPs and diseases unreliable? Suppose a gene-test company is looking at 1 million SNP variations. That means it’s still missing at least 90% of the total variation, says Lennon. Looking for links to disease among just a million SNPs “is the equivalent of looking under the lamp post for lost keys,” says J. Craig Venter, who led the race to decode the first human genome. Sure, the light is better there, but the keys are probably elsewhere. A SNP “doesn’t tell you whether you will get the diseases,” Venter says. What’s more, researchers have barely begun to take into account more important differences in people’s genes, such as extra copies of some genes, or rearrangements or deletions within others.

Indeed, many purported links don’t hold up in subsequent studies. “I tend to be very skeptical,” says Vanderbilt University statistician Frank E. Harrell Jr. “My wild guess is that only about 15% of the findings are reliable.”

DESIGNER GENOMES

23andMe CEO Linda Avey readily admits the science is still in its early days. “We are the first to say this is just the beginning,” she says. “The mission of the company is to do research,” Avey adds, collecting data on its own customers to find and better pin down associations between genes and disease. But she also insists that people already benefit from the information by the company, which has held high-profile

“spit parties” where celebrities give saliva samples to be tested at a discount. “To say that SNP associations have little value is ridiculous,” she says. Besides, she adds, 23andMe will progress to full gene sequencing “when the time is right.”

Yet science is telling us that even whole genes aren’t perfect predictors. Last year, cardiologist Dr. Eric Topol, a genomics professor at the Scripps Research Institute, started a project to look at the “wellderly”—elderly people who have always been healthy. The idea is to avoid the lamp post problem by reading their entire genetic code. The big surprise is that all these people seem to have just as many “bad” genes as average folk. “We find that they carry lots of bad genes, for Alzheimer’s, heart disease, for various cancers,” Topol says. “What’s interesting

pare that with each person’s full medical history. “This is a far bigger challenge than sequencing the human genome,” says Venter. The final bit is yet harder: figuring out the epigenetics. How do different environments and choices affect the genes? “All this complexity doesn’t make a good story,” says Lennon.

The gene-testing companies acknowledge the limitations but insist they still offer value. “If we postpone until we have more information, we are not taking advantage of what we know,” says Dr. Kari Stefansson, CEO of deCODE. “I have no question that within five years, most college-educated people will have a genetic profile of themselves.”

Yet many scientists believe that unless Navigenics, 23andMe, and others can make the transition from SNP testing to more complete genome work and find a way to overcome the many complexities, they won’t be able to go public or make money for their investors. Lennon’s own history shows how biotech fads have foundered on the shoals of biology’s complexity. He was chief scientific officer of a gene startup that soared and crashed, and CEO of a stem cell company that shut down when the science didn’t pan out. “There’s tremendous pressure on [biotech startups] from their investors for a fast return,” he warns. “That creates a clear conflict and tension.”

There are already signs of such strife in direct-to-consumer gene testing. In early September, 23andMe slashed the price of its test from \$999 to \$399. CEO Avey says the drop wasn’t brought on by lower-than-expected demand: “We are very happy with the volume of customers.” Instead, she says, the company is passing along reductions in the cost of the tests. Navigenics CEO Baker says she intends to hold to her \$2,500 price point—at least for now. DeCODE’s Stefansson says that his personal-genomics business, deCODEme, has started slowly, but says “sales are picking up gradually.” Other startups haven’t been able to afford to wait. In early October, Smart Genetics, a South Philadelphia company that tested for genes that could predict risks of Alzheimer’s disease, closed up shop. As for Greg Lennon, he’s still optimistic. “Trust me, someday your genome will be incredibly important for you to analyze. But today, for the average person, the test results can’t live up to their slick marketing.” **IBW**

“IF WE POSTPONE UNTIL WE HAVE MORE INFORMATION, WE ARE NOT TAKING ADVANTAGE OF WHAT WE KNOW,” SAYS DECODE’S CEO

is that they don’t get these diseases.” One reason why not: The wellderly may carry other genes, still undiscovered, that cancel out the risk from “bad” ones, says Topol.

Dr. Joseph Holoshitz, professor of medicine at the University of Michigan, is intrigued by a similar enigma in rheumatoid arthritis. More than 90% of people with the disease have a particular genetic marker or SNP. Now imagine a person who has both the marker and the disease and also has an identical twin. One would assume the twin probably also has arthritis. Nope. The actual likelihood is just 10% to 15%.

The solution to this puzzle may come from a relatively new field called epigenetics—peering beyond the genes. It turns out there are biological mechanisms for silencing certain genes, so they have no impact. One twin may get a disease while an identical twin, with exactly the same genes, does not. “If you have the DNA sequence, you have only half the information,” says J. David Sweatt, chair of neurobiology at the University of Alabama at Birmingham. “The epigenetics is the other half.”

Think of genes as the canvas on which the picture of a life is painted. For a few unfortunate people, the canvas comes with major rips and tears, causing inherited diseases such as cystic fibrosis. For most, though, the genetic variations are subtle lumps in the canvas that merely nudge people down certain paths or slightly raise risks for diseases. “The genome you are born with is just a tentative plan. How you execute it is up to you,” says Holoshitz.

That means, for companies such as 23andMe to deliver on their promises, scientists must first know a person’s entire genome, not just a few hundred thousand SNPs. Then they must com-

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Sequencing for Less

The true value of genetic information won’t be realized until researchers and companies can read the entire genetic code. That’s expensive today, but the cost is dropping fast, as Andrew Pollack describes in two stories in *The New York Times*. On Feb. 9, 2008, he chronicled the technological competition, focusing on an innovative approach from Pacific Biosciences. And on Oct. 6, Pollack zeroed in on how another company, Complete Genomics, hopes to lower the price to \$5,000 per genome.

Read these stories at <http://bx.businessweek.com/genetic-testing/reference>

