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Know your genes, know yourself

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J. Craig Venter, the former Celera Genomics president who led one of two efforts to decode the human genome, has a leg up on the rest of us. It seems the genome Celera decoded two years ago was primarily his own. So what? Well, for starters, Venter now is taking cholesterol-lowering drugs to counteract the potentially negative effects of a variant gene he spotted in his own DNA. Now that is personalized medicine.

For those of us without several years and a spare billion dollars to follow Venter's example, researchers are developing technologies that could someday deliver this kind of genetic self-knowledge to the masses. From the string of 3 billion "letters" in our DNA, each of us might learn which diseases we are susceptible to in time to take preventive action. If we got sick, person-to-person variations in our genes would guide doctors in choosing exactly the right allergy medication, antidepressant, or painkiller for us. Eventually, personal genomes could help athletes tailor their training, dieters draw up meal plans, and addicts map out recovery programs. In a couple of decades we might even carry digital cards encoded with our personal gene maps right alongside our medical insurance cards.

Such information won't do much good until scientists learn far more about how subtle DNA variations affect health--and how those predispositions can be overcome. Personal genomics will also require DNA-analyzing technology vastly faster and cheaper than exists today. But the race to develop it is already on.

Genetic tests are nothing new. Patients, prospective parents, and even fetuses can be tested for some gene variants, such as those linked to cystic fibrosis, metabolic problems, and certain cancer risks. But those tests are mostly slow and expensive, focusing on one or a handful of genes at a time. True personal genomics means examining the tens of thousands of genes strung out along the 6-foot length of human DNA. And full genome sequencing, although much faster than it was just five years ago, still takes a laboratory full of machines each analyzing a small part of the DNA, together with computers for stitching the results together.

But now that pioneering projects like Celera's have given scientists a portrait of the human genome, they can begin cataloging the person-to-person variations that help make each of us distinct. And they can set to work on miniaturized labs-on-a-chip that can rapidly scan an individual's genome for those variations.

Four years ago Eugene Chan, now 28, dropped out of Harvard Medical School to take up the quest. Earlier this year U.S. Genomics, the company he founded in Woburn, Mass., patented a process that would expose a person's entire genome to many different fluorescent markers, each designed to bind to a specific genetic variant along the DNA. Then the system would untangle the DNA and run it like a length of videotape past an optical reader on a chip. The reader would detect the presence or absence of each marker, cataloging the person's genetic idiosyncrasies. Within three to five years, Chan says, U.S. Genomics should be able to scan an entire human genome in 30 minutes. But other researchers point out major challenges, including developing an optical reader able to reliably detect the tiny fluorescent markers as they flash past, along with software capable of making sense of the data.

Across the country in Silicon Valley, Agilent Technologies is working on an even more ambitious scheme to

sequence individual genomes letter by letter, as the DNA molecule snakes through an infinitesimally small hole in a membrane. Each chemical unit passing through the hole would block it by an amount that depends on the unit's shape, reducing an electric current passing through the hole. The current's ups and downs would be translated into a complete DNA sequence. Although the technology looks promising in theory, it faces a serious stumbling block: Agilent has not yet figured out how to make a hole that is reliably small enough--about 2 nanometers across, one tenth the size of a virus--to hold a DNA strand snugly.

Until technology can serve up a complete personal gene map, some start-ups are introducing individuals to small parts of their genetic blueprints. In Britain, a company called Sciona charges consumers about \$180 for a "nutrigenomic" service: a set of conventional tests for genetic variants that influence metabolism, coupled with dietary and lifestyle recommendations based on the test results. And a Colorado start-up called NeuroMark soon will offer what it calls neurobehavioral gene maps: individual screens for 20 to 50 key genes believed to influence addiction, depression, anxiety, and even unwanted weight gain.

NeuroMark will base its service on powerful miniaturized laboratories called DNA microarrays--tiny glass chips patterned with genetic snippets corresponding to dozens, even thousands, of gene variants. When a person's DNA sample is applied to the chip, any of those variants present in the DNA will bind to the matching snippet, generating an optical signal. DNA microarrays have mainly been research tools, and their use for gene profiling would be a big step toward personal genomics.

Subtle influences. Yet Jeffrey Kahn, director of the Center for Bioethics at the University of Minnesota-Twin Cities, worries that customers of NeuroMark and other companies may be disappointed. Most of the genetic variations linked to depression, addiction, and even cancer have only subtle influences on health. "So if people learn that they have a 10 percent greater risk than average for colon cancer, does that mean they should eat less red meat and more fiber?" he asks. "That's probably good health advice for just about everyone." And Kahn warns that advice based on current understanding about genetic influences may be reversed after further research.

Harvard University genetics Prof. George Church, on the other hand, is thrilled by the prospect of personal genomics. The more we know about ourselves, he reasons, the more we'll be interested in finding treatments for genetic ailments, in essence creating "community involvement in our own bodies." Information is power, he says. "If I found out I have a 50 percent chance of getting Alzheimer's prematurely, I might want to become an advocate for Alzheimer's research or change my diet or lifestyle to stave it off," he says. "This is not genetic determinism. It's not destiny."

Concerns about privacy, in-utero testing and abortion, insurance discrimination, and even employment discrimination may hamstring the personal genomics revolution before it gets started. But if those issues can be resolved and the scientific hurdles can be overcome, even Kahn agrees about the ultimate potential. "The genetic revolution may eventually give us personal health profiles that will help us lead better and healthier lives," he says.

Speed-reading DNA

Two technologies under development would rapidly scan an individual's entire DNA, threadlike molecules 6 feet long when untangled.

[Drawings are not available]

[Drawing labels for first method]

Narrow passage

One technique would pass DNA through a tiny pore in a membrane, sensing the distinctive shape of each chemical letter as it passes.

Salt solution

Membrane

Pore

Electric current

Negative charge

Positive charge

Current: Low; High

1 A charge difference across the membrane causes an electric current to flow through the pore.

2 As single or double stranded DNA is drawn through, its components block the opening by differing amounts, causing detectable drops in current.

Play of light

[Labels for second method]

Another technique relies on fluorescent tags, which bind to and identify stretches of DNA that vary from person to person.

1 Fluorescent tags applied to the DNA molecule bind to genetic variations.

2 As the DNA passes through a special chip, a laser causes each tag to glow, allowing an optical reader to detect it.

DNA

Reader

Laser

Glowing tag

Sources: Agilent Technologies (top); U.S. Genomics (bottom); STEPHEN ROUNTREE AND DOUG STERN--USN&WR

A coming era of personal genomics could bring DNA profiling to the masses

Picture: QUICK STUDY. Eugene Chan holds a prototype of the high-speed DNA-scanning device his company is developing. (RICK FRIEDMAN); Drawings: Speed-reading DNA (Agilent Technologies (top); U.S. Genomics (bottom); STEPHEN ROUNTREE AND DOUG STERN--USN&WR)

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