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23AndMe Will Decode Your DNA for $1,000. Welcome to the Age of Genomics

By Thomas Goetz 11.17.07

At the age of 65, my grandfather the manager of a leather tannery in Fond Du Lac, Wisconsin, suffered a severe heart attack. He had chest pains and was rushed to the hospital. But that was in 1945, before open heart surgery, and he died a few hours later. By the time my father reached 65, he was watching his diet and exercising regularly. That regimen seemed fine until a couple of years later, when he developed chest pains during exercise, a symptom of severe arteriolosclerosis. A checkup revealed that his blood vessels were clogged with arterial plaque. Within two days he had a triple bypass. Fifteen years later (15 years that he considers a gift), he's had no heart trouble to speak of.

I won't reach 65 till 2033, but I have long assumed that, as regards heart disease, my time will come. My genes have predetermined it. To avoid my father's surgery, or my grandfather's fate, I try to eat healthier than most, exercise more than most, and never even consider smoking. This, I figure, is what it will take for me to live past 65.

Turns out that my odds are better than I thought. My DNA isn't pushing me toward heart disease — it's pulling me away. There are established genetic variations that researchers associate with a higher risk for a heart attack, and my genome doesn't have any of those negative mutations; it has positive mutations that actually reduce my risk. Like any American, I still have a good chance of eventually developing heart disease. But when it comes to an inherited risk, I take after my mother, not my father.

Reading your genomic profile — learning your predispositions for various diseases, odd traits, and a talent or two — is something like going to a phantasmagorical family reunion. First you're introduced to the grandfather who died 23 years before you were born, then you move along for a chat with your parents, who are uncharacteristically willing to talk about their health — Dad's prostate, Mom's digestive tract. Next, you have the odd experience of getting acquainted with future versions of yourself, 10, 20, and 30 years down the road. Finally, you face the prospect of telling your children — in my case, my 8-month-old son — that he, like me, may face an increased genetic risk for glaucoma.

The experience is simultaneously unsettling, illuminating, and empowering. And now it's something anyone can have for about $1,000. This winter marks the birth of a new industry: Companies will take a sample of your DNA, scan it, and tell you about your genetic future, as well as your ancestral past. A much-anticipated Silicon Valley startup called 23andMe offers a thorough tour of your genealogy, tracing your DNA back through the eons. Sign up members of your family and you can track generations of inheritance for traits like athletic endurance or bitter-taste blindness. The company will also tell you which diseases and conditions are associated with your genes — from colorectal cancer to lactose intolerance — giving you the ability to take preventive action. A second company, called Navigenics, focuses on matching your genes to current medical research, calculating your genetic risk for a range of diseases.

The advent of retail genomics will make a once-rare experience commonplace. Simply by spitting into a vial, customers of these companies will become early adopters of personalized medicine. We will not live according to what has happened to us (that knee injury from high school or that 20 pounds we've gained

since college) nor according to what happens to most Americans (the one-in-three chance men have of getting cancer, or women have of dying from heart disease, or anyone has for obesity). We will live according to what our own specific genetic risks predispose us toward.

This new industry draws on science that is just beginning to emerge. Genomics is in its earliest days: The Human Genome Project, the landmark effort to sequence the DNA of our species, was completed in 2003, and the research built on that milestone is only now being published. The fact that any consumer with $1,000 can now capitalize on this project is a rare case of groundbreaking science overlapping with an eager marketplace. For the moment, 23andMe and Navigenics offer genotyping: the strategic scanning of your DNA for several hundred thousand of the telltale variations that make one human different from the next. But in a few years, as the price of sequencing the entire genome drops below $1,000, all 6billion points of your genetic code will be opened to scrutiny.

To act on this data, we first need to understand it. That means the companies must translate the demanding argot of genetics — alleles and phenotypes and centromeres — into something approachable, even simple, for physicians and laypersons alike. It's one thing for a doctor to tell patients that smoking is bad for them, or that their cholesterol count is high. But how are you supposed to react when you're told you have a genetic variation at rs6983267 that's been associated with a 20 percent higher risk of colorectal cancer? And what are physicians, most likely untrained in and unprepared for genomic medicine, to do when a patient comes in wielding a printout that indicates a particular variation of a particular gene?

This new age of genomics comes with great opportunity — but also great quandaries. In the genomic age, we will no longer have the problem of not knowing, but we will face the burden of whether we want to know in the first place. We'll learn what might be best for us in life and then have to reckon with the risk and perhaps the guilt of not acting on that knowledge. We will, counterintuitively, face even more pressure to conduct our lives carefully, strictly, and cautiously; we'll practice the art of predictive diagnosis and receive a demanding roster of things to avoid, things to do, and treatments to receive — long before there's any physical evidence of disease. And, yes, we will know whether our children are predisposed to certain traits or talents — athletics or music or languages — and encourage them to pursue certain paths. In short, life will become a little more like a game of strategy, where we're always playing the percentages, trying to optimize our outcomes. "These are enormously large calculations," says Leroy Hood, a pioneer of genomic sequencing and cofounder of the Institute for Systems Biology in Seattle, who suggests that if we pay attention and get the math right, "it's not a stretch to say that we could increase our productive lifespans by at least a decade."

The question was surely strange. In February 2005, Anne Wojcicki sat down at the so-called Billionaires' Dinner, an annual event held in Monterey, California, and asked her tablemates about their urine. She was curious whether, after eating asparagus, they could smell it when they urinated. Among those at her table were geneticist Craig Venter; Ryan Phelan, the CEO of DNA Direct, a San Francisco genetic-testing company; and Wojcicki's then-boyfriend (and now husband), Sergey Brin, cofounder of Google. Most could pick up the smell of methyl mercaptan, a sulfur compound released as our guts digest the vegetable. But some had no idea what Wojcicki was talking about. They had, it seems, a genetic variation that made the particular smell imperceptible to them.

Soon, the conversation turned to a growing problem: While researchers are amassing great knowledge about certain genes and genetic variations, there is no way for people to access that data for insights about themselves and their families — to Google their genome, as it were. As a biotech and health care analyst at Passport Capital, a San Francisco hedge fund firm, Wojcicki knew that the pharmaceutical industry was already at work on tailoring drugs to specific genetic profiles. But she was intrigued by the prospect of a database that would compile the available research into a single resource.

Linda Avey (left) and Anne Wojcicki founded 23andMe in 2006.
Photo: Brent Humphreys

Linda Avey wasn't at the dinner, but she wished she had been when she read about it later that year in David Vise and Mark Malseed's book, *The Google Story*. At the time, Avey was an executive at Affymetrix, the company that had pioneered some of the tools for modern genetic research. For nearly a year, she had been mulling the idea of a genotyping tool for consumers, one that would let them plumb their own genome as well as create a novel data pool for researchers. She even had a placeholder name for it: Newco. "All the pieces were there," Avey says. "All we needed was the money, as usual, and computational power." Two things that Google has plenty of. Around the time she read Vise and Malseed's book, Avey had a dinner scheduled with a Google executive. She asked Wojcicki to join them, and the two quickly hit it off. Within a few months, they had settled on the idea behind 23andMe: Give people a look at their genome and help them make sense of it. (The company's name is a reference to the 23 pairs of chromosomes that contain our DNA.)

Brin offered to be an angel investor. "Sergey was like, Come up with something in three months and launch it,'" Wojcicki says. "We thought it would be so fast." In fact, the project took more than 18 months from conception to launch. Last spring, Google invested $3.9 million in 23andMe (part of the proceeds repaid Brin, who has since recused himself from the investment). The company, which now has more than 30 employees in a building down the road from Google, feels very much like the quintessential startup. In the entry hall, alongside two Segways (a gift from inventor Dean Kamen), stands a herd of pedal-pusher bicycles. On a whiteboard in the hall, someone has scrawled an anxiety meter. *Current threat level: slight deformation* (engineering-speak for moderate stress). But that level had been crossed out and the alert upped to *bananas*.

Still, 23andMe is hardly a typical Valley outfit. Instead of widgets and Ajax apps, the cubicle chatter more likely concerns Klinefelter's syndrome and hermaphrodites. Such banter underscores a major challenge for the company: making customers comfortable with the strange vocabulary and discomfiting implications of genetics. As Avey notes, when you're asking your customers for their spit, best to have an especially strong relationship.

A lot of spit, as it turns out. It takes about 10 minutes of slavering to fill the 2.5-milliliter vial that comes in the fancy lime box provided by 23andMe. Wrap it up, call FedEx, and two to four weeks later you get an email inviting you to log in and review your results. There are three main sections to the Web site: Genome Labs, where users can navigate through the raw catalog of their 23 pairs of chromosomes; Gene Journals, where the company correlates your genome with current research on a dozen or so diseases and conditions, from type 2 diabetes to Crohn's disease; and Ancestry, where customers can reach back through their DNA and discover their lineage, as well as explore their relationships with ethnic groups around the world. Family members can share profiles, trace the origin of particular traits, and compare one cousin's genome to another in a fascinating display of DNA networking. Avey herself has had roughly 30 members of her

extended family genotyped, spanning four generations. The effort has turned her clan into what is likely the most thoroughly documented gene pool in the world.

It's the Gene Journals, though, that could really change people's lives. Here customers learn their personalized risk for a particular condition, calculated according to whether their genotype contains markers that research has associated with specific risks. Wojcicki stresses, though, that 23andMe's results are not a diagnosis. "It's simply your information," she insists. In part, this distinction is to make sure the company doesn't run afoul of the Food and Drug Administration, which strictly regulates diagnostic testing for disease but has been slow to respond to the more transformational aspects of genomics. But the caveat also matters because the influence of genetics varies from disease to disease; some conditions have a strong heritable component, while others are determined more by environmental factors.

With its emphasis on disease risks, Navigenics is more comfortable offering something closer to a diagnosis. "If I tell you you've got a genetic likelihood of getting colon cancer, you're going to get a colonoscopy early," says Navigenics cofounder David Agus, a prominent oncologist and director of the Spielberg Family Center for Applied Proteomics at Cedars-Sinai Medical Center in Los Angeles. "And that's going to save lives."

Both companies draw a good lesson from the bad example of the body scan industry. When storefront CT scanning machines popped up in the late 1990s, the idea seemed golden to many radiologists and entrepreneurs: Customers could go directly to an imaging center and get an early look at possible tumors or polyps for about $1,000. But the market cratered by 2005, when it became evident that insurers wouldn't pay for the scan without a prior diagnosis and customers wouldn't pay out of pocket for frequent scans. What's more, the false-positive rate was jarringly high, and anxious customers often raced back to their doctor with an image showing, for instance, benign kidney or liver cysts, only to be told that they were harmless incidental lumps.

In other words, there was too much noise and not enough signal. So both 23andMe and Navigenics are determined not to simply shovel along raw research, with scary one-off results indistinguishable from well-established correlations. In-house experts at both companies have filtered and vetted hundreds of studies; only a handful are deemed strong enough to incorporate into their library of conditions, which is used for personalized risk calculations. The hope is that this will reduce or eliminate false alarms and let customers trust the experience — maybe even enjoy it.

One afternoon I was working up my own 2.5 milliliters of spit at the company's office when Jimmy Buffett dropped by to get an early peek at his results. A few month's earlier, the singer had let 23andMe peruse his genotype and compare his genealogy to Warren Buffett's. The two men had long wondered if they were somehow related (they aren't, it turns out). Now Jimmy wanted to check out the whole experience. He sat down in front of a laptop in Wojcicki's office, and she looked over his shoulder, guiding him through the site. First he clicked through his ancestral genome, noting that his maternal lineage showed a strong connection to the British Isles. "So the women came over with the Saxon invasion; pretty cool," he said. Another click and he perused his similarity to other ethnic groups, spotting a strong link to the Basque region of Spain. "No wonder I like Basque food so much," he noted.

Then he clicked over to see his disease risks — and was transfixed. "Wow. Right, that's about right for my family," he said as he ran through various conditions. After about 45 minutes of self-discovery, he leaned back in his chair to put it all together. "Boy, this can get pretty fascinating. And every time some research comes out, I can log on and see how it works for me. I get it," Buffett said with a laugh. "You guys are mad scientists."

Gregor Mendel began growing peas in his abbey garden in the 1850s, just a simple monk curious about the differences among the plants. A member of the Augustinian order, Mendel took to his garden experiments with characteristic discipline and rigor. He grew some peas with green seeds and others with yellow ones, some with violet flowers and others with white, some with round seed pods and others with

wrinkled pods, and so on — at least 10,000 plants in all. By the time he was done, he had established the principles of genetic inheritance, identifying some traits as dominant and others as recessive. (Less celebrated is his later work breeding honeybees; though his hybridized African and South American bees produced wonderful honey, they were exceptionally vicious, and he destroyed them.)

More than a century later, Mendel's basic concepts remain the cornerstone of genetics. We now understand his traits as genes, and genes as sections of DNA — a strand of 3 billion pairs of ATGC (adenine and thymine, and guanine and cytosine), the nucleotides that compose our genome.

Since 1983, when the gene associated with Huntington's disease was first linked to a particular chromosome, most genetic discoveries have worked like Mendel's peas: They have focused on traits associated with single genes. These so-called monogenic conditions — diseases like hemochromatosis (where the body absorbs too much iron) or Huntington's disease — are easy to research, because the associations are pretty much binary. If you have the genetic mutation, you're almost certain to develop the disease. That makes them easy to screen for, too. There are now tests for more than 1,400 of these diseases: prenatal screening for cystic fibrosis, mutations in BRCA1 and BRCA2 genes that convey a strong risk for breast cancer, and so forth. This is the sort of genetic testing most of us are familiar with. And such screening can be extremely useful. Careful testing for Tay-Sachs disease among Ashkenazi Jews, for instance, has led to a 90 percent reduction in the disease in the US and Canada.

But as genetic research has progressed, the idea that most diseases will have a clearly defined, single genetic component — what's known as the "common disease, common gene" hypothesis — has turned out to be mostly wishful thinking. In fact, the 1,400 conditions that are currently tested for represent about 5 percent of diseases in developed countries, meaning that for 95 percent of diseases there's something more complicated going on.

Most conditions, it turns out, develop from a subtle interplay among several genes. They are said to be multigenic, not monogenic. And while scientists have made progress connecting the deterministic dots between rare genes and rare conditions, they face a far greater challenge understanding the subtler genetic factors for those more common conditions that have the major impact on society. "We're learning plenty about the molecular basis of disease — that's the revolution right now," says Eric Lander, founding director of the Broad Institute and one of the leaders of the Human Genome Project. "But whether that knowledge translates into personalized predictions and personalized therapeutics is unknown." In other words, not all genes are as simple to understand as Mendel's peas.

The source of this complexity lies in our SNPs, or single nucleotide polymorphisms, the single-letter mutations among the base pairs of DNA — swapping an A for a G, or a T for a C — that largely determine how one human is genetically different from another. Throughout our 6 billion bits of genetic code, there are millions of SNPs (pronounced "snips"), and some untold number of those play a role in our predilection for disease. For researchers like Lander, the main challenge is establishing which SNPs — or which constellation of SNPs — affect which conditions.

Consider, for instance, the many ways that a human heart can go bad. The arteries supplying blood to the heart can be clogged with plaque, constricting blood flow until the organ goes into arrest. Or a valve in the heart can leak, spilling blood into the lungs and causing pulmonary edema. Or the tissues of the organ itself can be weakened, as in cardiomyopathy, so that the muscle fails to pump enough blood throughout the body. Each of these conditions has specific terminology, causes, and treatments, but they are all versions of heart disease, which is the leading killer in the US. And each condition may have its own genetic component, or be influenced by a range of genetic components, with each case of the illness a unique combination of genetic variables and environmental factors. So establishing the genetic component of heart disease means, in actuality, accounting for a daunting variety of conditions and tracking the influence of a broad number of genetic variations, as well as separating them from environmental components.

Now, thanks to a series of complementary innovations, geneticists have begun teasing apart the complexity. First, the Human Genome Project, completed in 2003, provided a map for our common genomic sequence. Next, 2005 saw the completion of the first phase of the International HapMap Project, a less-celebrated but equally ambitious effort that cataloged common patterns of genetic variations, or haplotypes, SNP by SNP. That helped researchers know where they should focus their attention. And finally, by mid-2006 the price of genotyping microarrays — the matchbox-sized chips that can detect SNP variations from genome to genome — had dropped to a level that let scientists greatly increase the pace and scope of their research.

As these three factors have converged, the pace of discovery has taken off, producing a startling number of new associations between SNPs and disease. Even the sober *New England Journal of Medicine* described trying to keep up with the research as "drinking from the fire hose." Lander calls it a 20-year dream coming to fruition. "2007 has been one of those magical years where the entire picture comes into focus. Suddenly we have the tools to apply to any problem: cancer, diabetes — a huge list of diseases. It's just a stunning explosion of data. Pick a metaphor: We've now landed on this new continent, and the people are out there exploring it, and we're finding mountains and waterfalls and rivers. We're turning on lights in dark rooms. We're finding pieces to the jigsaw puzzle."

Clearly, this is an exciting time to be a geneticist. And, it turns out, a consumer, too.

Come late September, Avey and Wojcicki invited their board of scientific advisers to Mountain View, California, for one last review of the site before launch. The meeting began around noon. Avey, as is her habit, had been going strong since 4o'clock that morning. Wojcicki was less sprightly, having just returned the previous night from her three-week honeymoon with Brin on safari in Africa and sailing around Greece and Turkey; she was also coming down with a nasty cold. After some idle chat about the biology of sleep, the board watched a demonstration of the company's user interface. Soon, the discussion turned to the thorny question of how much 23andMe will have to teach its customers about genetics to enable them to understand its offerings. "If we can get them to understand LD, that'll be an accomplishment," Avey said, referring to "linkage disequilibrium," a fairly obscure term describing how some genetic variations occur more often than anticipated. No, said Daphne Koller, a Stanford computer scientist and 2004 MacArthur fellow. "This should be a black box. LD is just going to trip them up."

As it happens, because 23andMe is a Web-based company, it can do both, letting the genetics hobbyist geek out on the details while giving the novice a minimum of information. Still, the challenge here was palpable: Starting a personal genomics company isn't like starting a Flickr or a Facebook. There's nothing intuitive about navigating your genome; it requires not just a new vocabulary but also a new conception of personhood. Scrape below the skin and we're flesh and bone; scrape below that and we're code. There's a massive amount of information to comprehend and fears to allay before customers will feel comfortable with the day-to-day utility of the site. 23andMe's solution is to offer a deep menu of FAQs, along with some nifty animation that explains the basic principles of genetics.

But the startup is also careful not to overwhelm customers with foreboding information. Take its approach to monogenic conditions like Huntington's disease. For one thing, the company makes it clear that it is not in the diagnostic business and therefore doesn't provide specific genetic tests for specific diseases. But even if 23andMe wanted to, the SNP technology doesn't allow it, since many of the 1,400 monogenic conditions are diagnosed using techniques other than SNP testing. The BRCA1 and BRCA2 mutations that carry a high risk for breast cancer, for instance, are not SNPs but more complex defects that show up only in a test that sequences the entire gene. Similarly, the test for Huntington's looks for repeats of a certain nucleotide sequence, rather than single-letter variations. Given the rarity of such conditions, it would be cost-prohibitive to include these tests in a $1,000 run.

In other circumstances, the science is evolving so fast that 23andMe must invent a methodology as it goes. Take the essential task of calculating a customer's genetic risk for a disease, which the company delivers under its Odds Calculator. For a condition like type 2 diabetes, at least eight different SNPs have been correlated to the disease. Research among people of European descent has found that each of those SNPs

has a slightly different effect — a variation of rs4712523 can increase one's risk by 17 percent, while a variation at rs7903146 can decrease risk by 15 percent. To crunch these numbers and determine one person's risk factor, 23andMe has opted to multiply the risks together. But a competing school of thought argues for adding the risk from SNP to SNP. The two approaches can result in wildly different tallies. "A lot of this is unknown. It's totally experimental," Wojcicki told me a few weeks before the science board meeting. "No one has looked at all eight diabetes markers together. They've all been identified individually, but they don't know exactly how they work together. So we've tried to make that clear."

All the ambiguity is indeed clear. There's no lack of caveats and in-context explanations on the site counseling customers to be cautious. In fact, the board at times even urged the company to hedge less and embrace the technology's gee-whiz factor, including uncertainty, more decisively. George Church, the Harvard geneticist who pioneered the sequencing techniques behind the Human Genome Project, sketched out a scenario: When a new study reporting a genetic association with a disease shows up in *The New York Times*, people are going to log on to 23andMe that morning and check to see whether the genetic marker in question is in their results. "People are going to wonder if you've got them covered," Church said. "And the answer better be yes."

In fact, that answer depends on the DNA chip that 23andMe uses to scan customer genomes. The company outsources that work to Illumina, the chip's developer. In its lab, Illumina extracts DNA from saliva and disperses it across a 3- by 1-inch silicon wafer studded with more than 550,000 nanoscopic protein dots. Each dot detects a different SNP; more than half a million dots, strategically distributed across the human genome, cover a meaningful swath of anybody's DNA.

But it's possible that new research could turn up an association with a SNP that the 23andMe scan doesn't look for. And by definition, genotyping is a strategic, rather than an exhaustive, catalog.

The real endgame, therefore, is whole-genome sequencing, where you don't have to hope that you're covered — you'll know it. With whole-genome sequencing, all 3 billion base pairs of DNA will be identified: a complete library of your genetic code. As with DNA chips, sequencing technology is getting faster and costs are dropping. The Human Genome Project spent nearly $3 billion to sequence the first human genome. Sequencing DNA codiscoverer James Watson's genome cost just under $1 million; Craig Venter, who has already sequenced his genome at least once, is now spending about $300,000 to have it read again. Prices are expected to fall even more rapidly now that the X Prize Foundation has offered a $10million award to the first team to sequence 100 human genomes in 10 days for less than $10,000 each.

At the board meeting, as talk turned to whole-genome sequencing, the energy in the room picked up. "This is absolutely the future," said Michael Eisen, a computational biologist at UC Berkeley. "It's exactly what the company should be doing as soon as possible."

"We will," responded Wojcicki, who then offered a juicy detail to the board. "We already have 10 people lined up and willing to pay $250,000 each for their whole genome. It's definitely something we want to do, maybe even in '08."

"George, how much will $250,000 get you?" Eisen asked Church, who's also on the X Prize advisory board. "How good a sequence would that be?"

"As good as Watson's," Church said. "At least as good."

Pushing the science forward is also a key part of the 23andMe business plan. As the company builds up its roster of customer genotypes, and later whole sequences, it gains a treasure trove of data that in turn can drive further research. On signing up, customers agree that their data, though still confidential, may be made available for scientific purposes. As the pool of participants grows, the startup hopes to forge partnerships with academics and advocacy groups that focus on specific conditions. Already, the Parkinson's Institute is working with 23andMe on a study of Parkinson's disease. Similarly, 23andMe is

talking with Autism Speaks, an advocacy group, about initiating research into autism — a disorder so complex that it will require the genetic information of many thousand research subjects to tease out potential associations.

This is also where a novel use of social-networking tools comes in. Wojcicki envisions groups of customers coming together around shared genotypes and SNPs, comparing notes about their conditions or backgrounds and identifying areas for further scientific research on their own. "It's a great way for individuals to be involved in the research world," Wojcicki says. "You'll have a profile, and something almost like a ribbon marking participation in these different research papers. It'll be like, How many *Nature* articles have you been part of?'" (Social networking will be included in version 2.0 in a matter of months, Avey says.)

For the board, such enterprising approaches to research are part of the fun of 23andMe. But after a long afternoon in a stuffy conference room, even geneticists can tire of too much genetics, and the meeting wound down. As the group walked into the foyer, someone asked about the two Segways there. Soon enough, some of the world's most celebrated geneticists had hopped aboard and were taking turns racing around the office at top speed.

My risk for heart disease may be lower than average, but that doesn't mean my genome isn't primed for problems. Far from it. Variations of three SNPs double my risk for prostate cancer, leaving me with a 30 percent chance of developing it in my lifetime. Restless legs syndrome, a dubious-sounding ailment characterized by jerky twitches in the middle of the night, was recently associated with a particular SNP variation — and I've got it, raising my risk by 32 percent. And my risk for exfoliating glaucoma, a type of eye disease, is a whopping three times the average American's. While the average person has just a 4 percent risk, my risk factor of 12 percent means it's something to mind.

Scanning my spreadsheet, all the odds start looking more like land mines. An 18 percent risk festers for this potentially fatal condition, a 13 percent risk ticks for that debilitating condition, and somewhere out there looms a 43 percent chance for something I may survive but sure don't want. And suddenly I realize: I can try to improve my odds here and there — eat less steak, schedule that colonoscopy earlier than most — but I'm going to go somehow, sometime. I can game the numbers, but I can't deny them.

Think of it this way: Health is an equation, with certain inputs and outputs. With conventional medicine, that means some fairly basic algebra: the simple addition and subtraction of symptoms and causes, with treatments like pharmaceuticals and surgery on the other end of the formula. For most Americans, the calculation results in fairly good health, with a lifespan stretching into the seventies. With the advent of genomics, though, we have stumbled into a far more arduous calculus, one requiring a full arsenal of algorithms and vectors. It's a more powerful tool — but it's also a lot more complicated.

It's not just the matter of accounting for all of our genetic markers and computing the attendant risk. That's just the start of it. Real personalized medicine must take into account traditional environmental factors, like smoking and diet and exercise. It also must consider the legion of pathogens out there, each with its own genetic quirks — not only the conventional ones of infectious disease but also the emerging class of viruses that seem to influence conditions from certain cancers to ulcers to obesity. Then there is the microbiome, the trillion-cell ecosystem of microbes that lives inside all of us, contributing to our health in largely mysterious ways. Oh, and save a piece of the equation for epigenetics, changes to the ways genes function without changes in the actual gene sequence. They contribute to our risk for common diseases such as cancer, heart disease, and diabetes.

Finally, leave a big blank spot for chance. No matter how much we learn from our genome, no matter how much it explains about us, randomness is always a looming factor in any health equation. Consider one behavior that is strongly associated with bad health — smoking. Everyone knows smoking is the single worst choice most people can make for their health. Yet the truth is that about a quarter of long-term smokers will not die of a smoking-related disease. Fate doesn't always work in our favor, though: Account

for every known risk factor for heart disease — from high cholesterol to smoking to high blood pressure — and that explains only half the cases of the disease in the US. In other words, I can bank on my genes and live in the most optimal way... and still die of a heart attack.

Mathematics isn't just a metaphor here. All of these variables are being broken down into data by scientists, and each data set is being scrutinized in an effort to quantify its impact on health. So let's make the leap of faith. The science is there, the data has been crunched, and it's all clear: Your genome is telling you that you face an elevated risk for certain diseases. What do you do? First, you likely go to your doctor (and let's assume she is one of the mere 800 MDs nationwide who has some training in genetics, so that she can actually make sense of your information). She considers your elevated risk and recommends some specific changes to your lifestyle. Will that work?

It might, if you act on that advice. But odds are you won't. In 1981, the National Institutes of Health completed a 10-year study that stands as the largest effort in scientific history to track behavior change. Starting with a pool of more than 360,000 Americans, the NIH set up centers around the country to study how well people would follow behaviors to alleviate the risk of heart disease. The subjects received personal counseling and support to help them stop smoking, eat better, and lose weight. At the study's end, though, 65 percent of the smokers still had the habit, half of those with high blood pressure still had it, and few had changed their diet at all. Subsequent studies have shown the same thing: Changing behavior is hard.

Luckily, there will be drugs tailored to work more effectively with our genetic quirks. These pharmacogenomics already exist: Herceptin specifically targets breast cancers that are caused by a growth protein from the HER2 gene, for instance, and more are in development. But taking a drug for several years, even one tailored to your DNA, can create a new set of disease risks and initiates a new trajectory of calculations.

The question becomes, then, whether you want to embark on this path of oddsmaking in the first place. Many individuals won't want to know what their genome has in store. Others will, only to join the worried well — those who live in fear of fulfilling their genetic destiny. And, of course, those genotyped or sequenced at birth won't have that choice; it'll already have been made for them.

Still, Wojcicki is onto something when she describes our genome as simply information. Already, we calibrate our health status in any number of ways, every day. We go to the drugstore and buy an HIV test or a pregnancy test. We take our blood pressure, track our cholesterol, count our calories. Our genome is now just one more metric at our disposal. It is one more factor revealed, an instrument suddenly within reach that can help us examine, and perhaps improve, our lives.

Deputy editor Thomas Goetz (thomas@wiredmag.com) *wrote about diagnostic medical devices in issue 15.08.*