The Burden of Knowing

For the right fee, a Cambridge firm called Knome will unravel all the secrets hiding in your genes. But what happens when those secrets include a higher risk of getting cancer? Or of contracting a crippling disease like Alzheimer's? Would you be able to handle that information and the terrible choices it forces? I wasn't.

By Catherine Elton

January 2009

The flash drive comes in a silver box, sunken into a bed of black velvet, shining out, fittingly, like a rare gem. Fail 10 times to provide the correct password and the drive will self-destruct. The entire sequence of its new owner’s genome is inside this piece of brushed steel, all of his or her DNA. The Cambridge-based company selling the drive, Knome, is the only company in the world to offer anything like it. Only a handful of people in the world have one. For now.

The man responsible for Knome and the services it offers—services that will fundamentally alter the way we think about healthcare—is George Church, a 6-foot-5, bushy-bearded Harvard Medical School professor and the patriarch of personal genomics. His coming movement will wrest the genome from research labs and place it in the hands of the people, much as computers went from government and academia to being an inextricable part of daily life. The newer and faster technologies Church and his ilk are developing have already dropped what Knome charges for sequencing from $350,000 to $100,000. Church’s ultimate goal is to get the price down to $1,000, a price accessible for nearly everyone. When it reaches that point, he predicts, the genomic revolution will usher in an age of personalized medicine, in which doctors tailor treatments to a patient’s genetic makeup, to the individual strips of code that can serve as a marker for future diseases. It will allow patients an opportunity to truly—as the Knome motto goes—"Know thyself."

Not everyone is greeting the revolution with outstretched arms. A chorus of doctors, ethicists, and even some of Church’s fellow geneticists say that personal genomics is a wildly unregulated and woefully immature field, one in which science’s ability to read genes, and Madison Avenue’s ability to hawk its tests, is eons ahead of medicine’s understanding of the results. When doctors do understand them, there is often no preventive measure consumers can take to

head off their fate, if that fate is a disease like Alzheimer's or Huntington's. There's also the fear that personal genomics may not only one day customize medicine to our genes, but also custom-design our children. The question for people who oppose Church is whether this world of his is any place for the rest of us.

George Church found his calling as a 19-year-old college student at Duke University. He was working in a lab, playing around with a program used to make three-dimensional models of RNA molecules. This was in 1974, when computers could do little more than show a 3-D image. He decided to type in thousands of RNA bases, which direct the function of the RNA molecule. These bases are encoded by the A, C, T, or G proteins that make up the rungs of one's DNA. It took hours for him to type in the sequences before the machine spit back an image, which looked like strings of beads that folded back on themselves and then up until they resembled "little statuettes," Church says. The connection between the linear sequence of DNA and the encoded shape and form it took on the screen was an epiphany for him. He pictured an age in which computers could map the whole of each person's genomic sequence and translate it into his or her physical traits. Church vowed that day to spend his life bending the revelatory power of microprocessors to his will.

The moment set him on a career track that combined two of his childhood passions: biology and technology. As a boy Church had passed a lot of time alone, trapping and studying bugs from the ponds of his Florida island home and building basic computers from kits and spare parts. Something far less idyllic, seldom discussed but originating, too, in his boyhood, steered his early work as well. Church's father walked out on him and his mother when Church was a few months old, taking with him Church's sense of identity. "Because my first father left me when I was so young, I was never really quite sure who I was," he says. "And I had this feeling that people in general didn't know who they were, even if they lived in a nice nuclear family with all their grandparents nearby." The genome became to Church "this big missing thing," without which no one could truly understand himself. (Today, though the official pronunciation of his company is "nome," Church insists on mispronouncing it as "know-me.")

The quest to find this missing piece explains Church's impatience. He wrapped up his undergraduate degree from Duke in two years. He began his research-heavy graduate work there immediately and soon was spending 100 hours a week in the lab. He skipped classes, missed exams. And flunked courses. In 1976 he was expelled.

The following year, Harvard gave Church a second chance. There he started working under Nobel Prize–winning chemist Wally Gilbert, developing with him a new DNA-sequencing method, work that in turn led Church, at a meeting in 1984, to discuss ideas that ultimately became the Human Genome Project. But in the end, Church was disappointed that the 13-year, $2.7 billion undertaking chose to use existing technology to sequence one human genome. He all along had bigger goals in mind.

Before the Human Genome Project was completed in 2003, the scientists involved discovered that gene mutations—missing or repeated letters in the code of a gene—could be linked to certain diseases, and doctors began offering patients genetic tests for them. And yet apart from these mutations, most scientists didn't know (and still don't know) what most genes did. Put another way: They had come close to transcribing the entire book of life, but their proficiency in the language didn't go much beyond "I seem to have lost my luggage" and "Where's the bathroom?"

Church wanted to push toward fluency. In 2004, at his Harvard Medical School lab—the Center for Computational Genetics, one of the largest research labs in the Longwood Medical Area—Church began to design the Personal Genome Project. It would sequence a portion of the genomes of 100,000 volunteers, gather their medical records and note their personal traits, and make it all publicly available for scientists the world over in the hopes that they would make associations between genetic variations and health outcomes—that they would begin to fully understand what the "words" of the language of life really mean.

As Church talked about his project, he started to receive messages from people with a common request: They wanted Church to sequence them. Some had diseases in their families for which science had been unable to find a genetic cause. Others were potential investors in the field. All were extremely wealthy. But Church didn't want to do such

work in his academic lab, so he got together with a young biotech executive, Jorge Conde, with whom he had worked before, and serial entrepreneur Sundar Subramaniam. In November 2007 Knome was launched, offering complete sequencing at its original $350,000 price tag.

Today, by contrast, there are three other companies—deCodeme in Iceland and 23andme and Navigenics, both in California (and both backed by Google)—providing economy-class genome scans. They all use a cheaper technology to seek out single nucleotide polymorphisms, or SNPs (pronounced "snips"): genetic variants that have been statistically correlated with various traits and diseases. Customers pay as little as $400 to mail in a sample of their saliva. In about a month's time, they can log in to their account on the company's website and see whether they have, for instance, a 2 percent greater-than-average risk of getting diabetes, or a 20 percent lower chance of a heart attack.

The market for genomic analysis is still in its infancy, but by offering complete sequences, Knome has secured a reputation as the first-class player in the industry. The company says it met its target of landing 20 clients in its first year of operation. Knome's customers receive hours of initial counseling and information on what science can and cannot tell them about the contents of their genome. Then, once a client has wired half the fee to Knome's account, the company dispatches a physician to meet him or her—anywhere in the world—and collect four vials of blood. The DNA is extracted in New Jersey and sequenced in China. Back in Knome's Kendall Square headquarters, a stable of bioinformaticians pore over the data and cross-reference it with the most up-to-date genetic research. Taking advantage of its Cambridge location, Knome often asks other local genetic researchers to discuss with the company a particular aspect of a client's genome.

Then it's showtime. The client is flown in, with his doctor if he chooses, to meet the company's scientists (accompanied by Church himself when his schedule permits) for a daylong, one-of-a-kind, high-tech "me show" at Knome. The client takes home a binder, a few inches thick, with details about his or her genome and, of course, the flash drive with his or her sequence downloaded on it, to keep and cross-reference with every new genetic discovery.

For now, Knome and its genetic profiling counterparts remain privately held. No company will talk about its financials, and no in-depth analysis of this young industry exists. But Bruce Carlson, the publisher at Kalorama Information, a medical-market research firm, says there's little doubt personal genomics will be a "very profitable" field. "The problem won't be [lack of] customers," he says.

That's what Church is betting on. As he and other scientists improve the technology, which will in turn lower the price of complete sequencing to $1,000, he hopes that everyone will want the service. Of course, Church assumes that the expense of sequencing is the big obstacle to his vision becoming reality.

When I was 25, in 1997—ancient history in the world of genomics—I was invited to have one of my genes sequenced as part of a Dana-Farber Cancer Institute study. The gene in question is known as BRCA1; a mutation on that gene means a woman has, on average, a 60 to 80 percent greater chance of getting an aggressive form of breast cancer, and a 40 percent chance of developing ovarian cancer. My aunt tested positive for the BRCA1 gene mutation after she got breast cancer, but before she died of ovarian cancer. It's a mutation she likely got from my grandmother, who died of breast cancer. It's a mutation doctors assumed led to the ovarian cancer that killed my mother, when she was 33 and I was five.

At the time of the study I was living in Washington, DC. I met with two genetic counselors at a hospital there who were collaborating with Dana-Farber. They told me I had a variety of options if I tested positive. Because women with the BRCA1 mutation tend to get breast cancer at an early age, I could start mammograms at 30, a decade younger than most women. I could take birth control pills to lessen the risk of ovarian cancer, and schedule pelvic ultrasounds. None of this was different from what I was doing, or would be doing soon.

The counselors then mentioned another option: having my ovaries taken out and my breasts removed. Here we were, talking about science's ability to look along a submicroscopic piece of DNA, searching for missing letters on a strip of a gene, and yet if science found that letters were missing—if the gene had the cancer-risk mutation—the best it could do was amputate or sterilize. These options

seemed as though they should have been filed away in a medieval remedy book, somewhere between leeches and bloodletting.

I didn't want what I would learn from this test to shape the many life decisions I had yet to face. I didn't want a mutation to rush me into marrying the wrong guy, or having kids when I wasn't ready, or having fewer kids than I might otherwise—all because I might get cancer.

The genetic counselors asked if I was concerned about passing on the BRCA1 mutation to any children I might have. I was taken aback by the question. It seemed to suggest that your genetic draw could be reason enough to never have kids. That was followed by the reassurance that I could harvest, fertilize, and freeze my eggs before having my ovaries removed, and then, if I were to have my eggs implanted, choose among zygotes free of the BRCA1 mutation. By now I was disgusted. Following that logic, certain embryos deserved to be tossed off the edge of a petri dish, lest any become a baby who might get a disease as an adult that may or may not kill her. Furthermore, it meant that people deemed genetically unfit included my brilliant, loving, gorgeous mother. And, quite possibly, me. When it came time to give my consent to analyze my blood, I decided to decline.

Marcy Darnovsky is the associate director of the Oakland, California–based Center for Genetics and Society and has been an outspoken advocate for the oversight and responsible use of biotechnology. She says personal genome companies' aggressive marketing, slick advertising, and portentous mottos (like Knome's "Know thyself") have a "very important, if subtle, effect" of over-emphasizing the role DNA plays in who we are. She believes they're promoting a culture of genetic determinism, in which we risk losing sight of the environmental and social causes of diseases and our own ability to do something about them. That shift, she fears, could speed us into a world of high-tech eugenics. "We should take a look at lessons of history," she says, "when we start thinking about the future trajectory of new technologies."

Many others share Darnovsky's concerns about the lack of oversight of this emerging market. "It's not like what happens with drugs, where you can't throw something out there saying it cures cancer unless you have the data to back it up," says Gail Javitt of Johns Hopkins's

Genetics and Public Policy Center, which pushes for the legal system to keep pace with genetic invention. "There is no external third party evaluating the quality of these tests." The FDA has the authority to monitor them but does little to monitor the field.

So far, state governments have been the only ones to take action. New York has banned 37 companies, including Knome, from doing business there until they comply with state law. California has sent cease-and-desist letters to Knome and 13 other companies, demanding they get licensed. (The state has since rescinded its letter to Knome.) In Massachusetts, the Department of Public Health is studying whether to regulate any company that provides genomics services to residents; it currently regulates only genetics tests performed in labs within the state.

Beyond these policy concerns are more-fundamental objections raised by a number of doctors, who say the science upon which the tests are based is flaky. Last year the American Medical Association adopted policy guidelines recommending against direct-to-consumer genetic testing.

If you own a car, chances are you also have car insurance. George Church envisions personal genomics as one day playing a similar role in our society: a hedge against the plausible but dreaded. He believes that everyone should get sequenced, if only because diseases are foreshadowed within our DNA. "It's better to learn it early, as early as possible," Church says, "because there might be things that you can do."

No Knome customers would speak to me for this story, and the company would not release information about its clients. But I was able to get the stories of a few people who've used Navigenics, the California-based company that does genetic scanning. The head of its genetic counseling staff, Elissa Levin, mentioned one woman whose scan indicated an elevated risk of colon cancer, a disease for which she had no family history. At 39 she hadn't thought of screening for it, nor had her doctor; that's something you don't start doing until you turn 50. Prompted by the results, she requested a colonoscopy, during which doctors found and removed a benign polyp. Had it festered there for a decade until a routine colonoscopy was called for, it likely would have grown into a potentially fatal tumor.

Another Navigenics client, a Cambridge health consultant named Craig (who asked that his last name not be used), said he wasn't fazed by the possibility of learning of diseases lurking in his future. With two grandparents who lived till they were 99 and one who died at nearly 90 (in a car crash), he thought he was "pretty much bulletproof."

The results from Navigenics informed him he had a slightly higher chance of getting type 2 diabetes and was three times as likely to develop macular degeneration. He also had an elevated risk of heart attack. He remembered that his other grandparent had died of one. Craig now tries to eat better; his wife, Krista, bought him a gym membership. Of course, he should be watching what he eats and working out anyway, "but once you are looking at your results on your computer screen," Craig says, "that kind of message is harder to ignore."

Initially, Krista was against Craig's getting the profile done. She thought it seemed like playing God. She certainly doesn't want to know the contents of her own DNA: Breast cancer runs through her family. "I am the kind of person who would get so stressed out by the news that it'd probably suppress my immune system, and I'd wind up getting cancer," she says. "What good would that do?"

This is a common refrain among people who don't want to test. What good is it to know you have a predisposition in your genetic makeup to an untreatable disease? For them, the looming threat of an agonizing death is a fate as bad as, or worse than, the illness itself. Church respects this point of view; the company requires its clients to complete intensive counseling before it accepts payment or takes a drop of blood. Still, Church says, even in the case of incurable conditions like Alzheimer's or Huntington's, "you can raise money to do research or encourage research, or offer yourself and your family as guinea pigs to test out new drugs. Whatever you want to do to get involved."

James Watson, one of the discoverers of DNA's structure, felt differently. He volunteered to be the first individual to be sequenced, in 2007. Watson made sure Jonathan Rothberg, the scientist who did the procedure, hid from him the results of the ApoE gene, a variation of which is associated with Alzheimer's disease. Rothberg was only too

happy to honor the request; he's since had his own genes sequenced, and refused to find out his own ApoE status.

A decade ago, a cousin of Rothberg's was tested for a genetic mutation that leads without fail to Huntington's. This cousin had already watched her sister suffer the ravages of the disease. She tested positive. But she wasn't prepared to make her expected cause of death the focal point of the rest of her able-bodied life. Instead, she killed herself.

A few years after I dropped out of the Dana-Farber study, I moved to Peru to be a freelance foreign correspondent. Not long after that, I found myself thinking about testing again. It was 2000, I was 29 years old, and though I still held philosophical reservations about testing, I was too sick not to consider it.

The stomach pains and diarrhea were awful. My sprints to the bathroom had gone on for too long—two years—to be a case of traveler's sickness. Yet no lab could find any microscopic stowaways living in my system. A homeopath suggested I stop taking birth control, thinking it could be contributing to my stomach problems. But a side effect of the pill was a reduced chance of developing ovarian cancer. I consulted my gynecologist, who thought that if I went ahead with the gene test I had backed out of in DC, and it turned out negative, I could safely stop taking the pill.

And so one day a doctor drew my blood and sent it off to be analyzed. I was, as before, not married and not thinking about kids, but I was now in a serious relationship. My boyfriend and I were about to move together to Guatemala, where I would receive the lab results by e-mail. I'm an optimist by nature, and I truly believed I hadn't inherited the mutation. I thought that because my mother died of cancer when I was a little girl, I had fulfilled a lifetime cancer-suffering quota.

I'd almost forgotten about the test when, weeks later, I saw the e-mail from my doctor titled "Results." I clicked it open: I'd tested positive. I remember thrusting my chair away from the desk, gasping. I felt as if I were falling.

A few weeks later I traveled back to the U.S. to see a genetic counselor near my parents' home in Connecticut. The counselor told

me the story of a pair of 20-year-old twins whose mother encouraged them to test for the gene. When they tested positive, their mom suggested they each get pregnant, immediately, even though neither was married or in love. They both had babies, then had their ovaries removed. It was after the counselor relayed all of this that she said it might be prudent to have my own ovaries removed soon, and certainly before the age of 35.

But I still thought it was crazy to do that when you still wanted to have children. Or to have a kid just to have one, with no father in the picture and little future for yourself. I thought there was a really fine line between avoiding death and ruining your life.

So my boyfriend and I got married when we were ready, in 2003. We got pregnant in late 2004. Soon after, I won a journalism fellowship, and he was accepted to a master's program at Brandeis. We moved to the Boston area when I was seven months pregnant, and in August 2005, Micaela was born. We talked about having another child, perhaps in another two years. Knowing the risk I was taking, after that second child I would close up shop, so to speak. Just having the plan in place made me feel safer.

I was 13 weeks into my second pregnancy and weeks shy of my 36th birthday when I felt it. I was in bed, my husband asleep beside me. My right arm was draped over my chest, the fingers of that hand resting lightly on the slope between the breast and rib cage. Without even really thinking about it, I started to press my fingers into my breast. There it was: a hard, knobby little thing. I checked the other side and didn't feel anything similar. I met with my midwife the next day. She thought it was likely dried milk from having recently weaned my daughter. But she suggested I see a breast surgeon, just in case.

The next afternoon, the surgeon stuck a fine needle into the lump and extracted some cells, which went to the hospital's lab for a rapid assessment. In the meantime, the doctor sent me down the hall for an ultrasound while she awaited word on the biopsy. The radiologist told me the same thing as my midwife, that she thought the lump was related to breastfeeding, but performed a complete scan of both breasts and armpits to be safe.

While I waited for all these results, I read a magazine, worried only about being late for dinner. Then the surgeon came into the waiting room, sat herself on the couch beside me, and informed me I had cancer. She took me to meet with another, more senior surgeon. He told me I could go through chemotherapy while pregnant, but it would be a lot "simpler" if I terminated the pregnancy.

In the days that followed, instead of going to parties for my husband's master's graduation, the two of us walked around our Belmont neighborhood and moped about our house, trying to keep our sobs from Mica, who was now nearly two years old. We talked about terminating a wanted pregnancy. We talked about what my husband would do if I were to die, and whether it would be better for him to be left with one or two children.

And somehow, in addition to all I was feeling—the desperate, breath-stealing fear, the profound sadness—I also felt guilty. Could I have avoided this? I'd chosen to live this way, flouting my genes and the risks they represented. But was that reckless? People close to me pointed out that perhaps I should have seen it all coming. Maybe I was the crazy one all along.

Word of my diagnosis spread quickly among family members. Some female relatives ran out and got tested for the BRCA1 mutation. One found out she was positive. Like me, she had a mother who'd passed away when she was younger. The news terrified her. She was married but didn't have children; she told me she and her husband didn't think they wanted any. After hours spent with a genetic counselor and much thought, she decided she would undergo a prophylactic double mastectomy and—like nearly 70 percent of American women who test positive for a BRCA mutation—elect to have her ovaries removed. She would become, in the parlance, a "previvor." She was 27 years old.

I respected her decision and didn't want to try to change her mind. So I didn't say much. But what I wished I'd said was this:
I didn't think I wanted children at 27, either. But now that I've become a mother, it's the achievement that most shapes my identity. And somehow, having my own child—my own flesh and blood, and, yes, some of my genes—this has brought my mother back to me and helped reclaim parts of my own shattered childhood.

Perhaps I didn't tell my relative any of this because I didn't think I was in a position to give advice. After all, I was the one who took the risk and got cancer; mine was the example she was so desperately trying to avoid. Afterward, she called once in a while to discuss things. "When I got sick…," she said one day last summer, before telling me a story. I can't remember the rest of what she said; what has stayed was that word, "sick." She was never sick. She had a mutation, not an illness. The only thing that happened is she found out about it.

My husband and I decided to have the baby. I went through four cycles of chemotherapy while pregnant, and Eliana was born healthy and with a full head of hair in October 2007. She smiles approximately 90 percent of the time. It has been over a year since I was diagnosed; the chances are quite low that the cancer will at some point reappear in terminal form elsewhere in my body. But with breast cancer, that chance is never zero.

In one of my last conversations with George Church, I shared my story. When I told him I had originally resisted testing, he told me that he understood that this information could change people's lives in "subtle and unpredictable ways" and that it's not an easy decision to make. When I told him I had later tested positive and decided not to have surgeries, or rush to have kids, he said some people are prepared to take more risks in life than others, adding, "There could be a genetic component to that, too." When I told him I had developed cancer, he said he was "very, very sorry."

People make decisions, Church said, and live with the consequences. But those consequences become our lives, and we end up becoming the decisions we make. We can never know what we would be like had we chosen differently. We can only imagine. Sometimes even that is difficult to do.

My relative is convinced that if she hadn't had her surgeries, she definitely would have gotten cancer. I tell myself that if I had tested earlier in life, I might not have had my older daughter, Micaela. And that if I had found the lump earlier, I would not have had Eliana. George Church tells himself his story, in which his technology is used only for good, where there is always something to be gained, and never lost, from more information about our genes, and where if

science can do something, it should. We all believe whatever it is that convinces us we've done the right thing. It's simply in our nature