



PERSONALIZED MEDICINE

Unlocking my genome: Was it worth it?

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Genome sequencing: A glimpse of the future

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One morning in October, I was frantically scrambling around my apartment, trying to find a thumb drive.

It's probably the most valuable thumb drive I'll ever have, and I couldn't believe I had misplaced it. It contains the blueprint of who I am: My genome. Or at least, all the ways my genes differ from other people's.

It turns out, in the grand scheme, we're all very, very similar, genetically: 99.9 percent of people's genes are identical. It's in that last one-tenth of 1 percent where we find all of human variation — those things that make us special: athletic abilities (not so much in my case), frizzy hair (unfortunately for me) ... and in some cases, a predisposition to disease.

I had set out in August to have my genome sequenced, mainly out of curiosity. There was no problem I was trying to solve or specific answer I was seeking. That puts me in the minority of people who have their genomes sequenced today. As my geneticist, Harvard Medical School's Dr. Robert Green, likes to tell me, I'm among a group of medical pioneers.

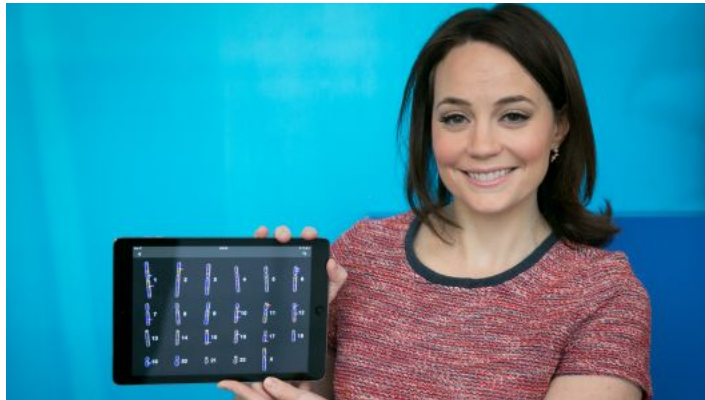
This made me feel very cool of course, but having your genome sequenced is a scary thing. What if I learned something dreadful? What if I was destined to get a disease that has no cure? What if I carried

mutations that could burden my future children with something awful? Did I really want to know?

Obviously, given my hunt for the thumb drive, the answer is yes. Our ability to map our own genes will be a bigger and bigger part of our medical care even in just the next decade. **President Barack Obama** has announced a Precision Medicine Initiative to accelerate what's possible using this genetic information. And already, gene sequencing is making major impacts on cancer care, diagnostics and drug development.

But it's still controversial how much genome sequencing is necessary, or even very useful on a personal level. Huge questions loom about cost, privacy and our own abilities to handle this kind of knowledge about ourselves.

I was about to find that out about myself.



Adam Jeffery | CNBC

CNBC's Meg Tirrell holds up her genome sequence on an iPad app by Illumina.

Getting sequenced

Because sequencing healthy people isn't a common medical practice, it's not all that easy to do. I participated in a program called Understand Your Genome, provided by sequencing company **Illumina**. For \$2,900, Illumina does what's known as a whole genome sequence, mapping every A, T, C and G that make up my 3 billion base pairs of DNA. (CNBC paid for the sequencing.)

Illumina also connected me with Green, my geneticist (whose visits were covered by my insurance).

"It's important for you to imagine what you would feel like if you learned that you had a mutation" that suggested I was headed toward some currently untreatable, disastrous disease, Green, who is associated with Brigham and Women's Hospital in Boston, told me the first time we met.

"Are you OK with that?" he asked. "Are you ready to learn that, if it falls that way?"

In truth, I wasn't sure how I would feel. I hoped my response would be a productive one, a kick in the pants to maximize the time I had, or, later in life, be better prepared for something like Alzheimer's.

But in actuality, it's more likely I was banking on the fact that it was exceedingly unlikely I'd be predestined for something like early-onset Alzheimer's, given how rare it is in general and the fact that it had never turned up in my family.

But as I discovered, it was also unlikely I'd learn something particularly useful, or "actionable," as geneticists describe it, a dominant mutation that would predispose me to a treatable cancer or heart disease, for example. (We have two copies of each gene; one from our mom, and one from our dad. A dominant mutation is one where only one copy is needed for its effects to be shown; a recessive one requires two copies.)

According to Green, only about 1 to 2 percent of people get an "actionable" result. That's in part, I learned, because we're still very much in the early days of interpreting our own genetic information, and in part because our genes don't determine everything about our lives.

"There is a great deal of debate about whether this is worth sequencing ... because it hasn't been proven that you can change something and change their outcome."

-Dr. Robert Green, Harvard Medical School geneticist

"There is a great deal of debate about whether this is worth sequencing a lot of people in order to find those few," Green said.

It seemed to me those few would certainly feel it was worth it. But, he said, "there is even debate about if you find those few, are you really going to help them, because it hasn't been proven that you can change something and change their outcome."

Variants of unknown significance

If it feels like genome sequencing raises more questions than it answers, that's due to a yawning gap between what sequencing technology enables us to discover, and how much we actually understand about the information we get back.

Because genome sequencing is so young, we only have a decade and a half of historical data from which to draw conclusions. Our understanding of all the implications of our genetics hasn't caught up yet to the power of sequencing technology.

So while up to 2 percent of people may get a finding they can do something with, 20 percent have some kind of dominant mutation without any sign of disease, Green said. That means they have a mutation researchers suspect would be tied to disease, but it hasn't actually manifested, and it's unclear if and how it will.

My report would come back with a section titled "Variants of Unknown Significance" — mutations for which there is limited evidence of

relevance to disease, but which can't confidently be counted out. I turned out to have two, listed as "suspicious," in terms of whether they were likely to cause disease. Not the most reassuring word to find on your genome sequencing report. But that's a function of how much we know about genes and disease.

"We have a big pile of genes that we can say are associated with schizophrenia or early-onset heart attack or many other things," said Dr. Eric Lander, director of the Broad Institute of Harvard and MIT. "But it's still hand-to-hand combat with the genes to figure out what they're actually doing."

The Broad is a nonprofit research institute that is, among other things, one of the world's largest genome-sequencing centers. Lander was also one of the leaders of the Human Genome Project, the 15-year odyssey to map the first human genome.

'Most wondrous map'

"Without a doubt, this is the most important, most wondrous map ever produced by humankind," President Bill Clinton said in his White House announcement at the culmination of the project. "In coming years, doctors will increasingly be able to cure diseases like Alzheimer's, Parkinson's, diabetes, and cancer by attacking their genetic roots."

That was June 26, 2000. Fifteen years later, we haven't seen those cures — at least, not in totality across disease. But researchers point to strides made particularly in cancer, where deciphering a tumor's genetic signature can point to more targeted treatments than chemotherapy, which essentially blankets the body with poison. And researchers bristle at the idea that these kinds of medical advances should have been immediate.

"You can point to all kinds of amazing things that are happening, but we're in this for the long run," Lander said. "And in the long run, it's a sequence of the genome, a genetic variation, all the genes responsible for it, the mechanism by which they work, the ways you could intervene ... and then therapies."

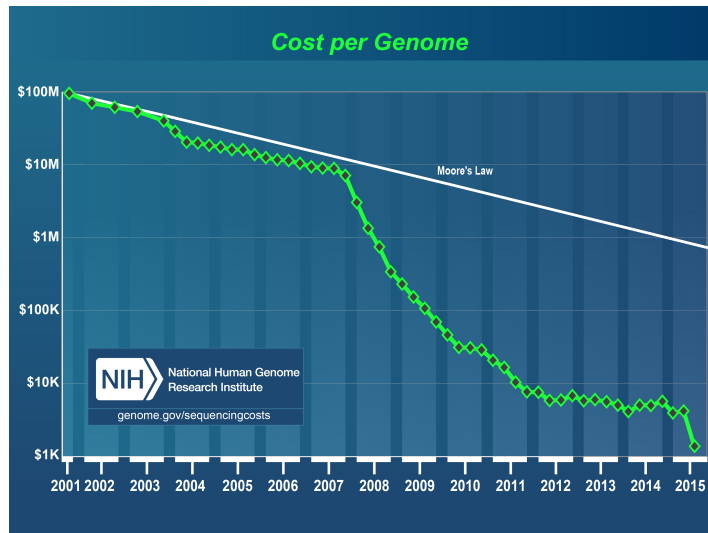
"I see this as a multidecade effort," Lander continued. "It is the work of the 21st century."

In that decade and a half though, much has changed. In particular, the cost of genome sequencing has come down dramatically.

Outpacing Moore's Law

Geneticists have a graph they love to show at conferences. It charts the cost to sequence one human genome against Moore's Law, the projection by Intel co-founder Gordon Moore that computing would increase exponentially in power while decreasing in cost.

It shows the cost to sequence a genome diverging drastically around 2008, falling from almost \$10 million to close to \$1,000 today.



The first human genome took \$2.7 billion and almost 15 years to complete. Now, according to Cowen analyst Doug Schenkel, genome sequencing and analysis cost around \$1,400. The sequencing can be done in a few days, and analysis in a few weeks, he said.

Much of that progress has been driven by companies including [Illumina](#), a San Diego-based provider of sequencing technology with a market value that's almost tripled in the last five years, to more than \$25 billion. The company is on track to record more than \$2 billion in sales this year, and projects its overall market opportunity to exceed \$20 billion.

One of Illumina's main competitors, Life Technologies, was acquired by [Thermo Fisher Scientific](#) in February 2014 for more than \$13 billion. Swiss drug company Roche also competes in sequencing, along with a handful of smaller players.

Jay Flatley, Illumina's chief executive, says the price of genome sequencing will continue to decline over the next five years.

"We haven't announced where we think they can get, but clearly getting to a \$500 genome is technologically possible," Flatley told me at a genetics conference in Baltimore. "And we think certainly there's potential far beyond that."



Tek Image | Science Photo Library | Getty Images

Precision Medicine Initiative

But the question still looms: What do we do with all this information? Massive efforts are taking place around the world to bolster our knowledge of genetics, and many hope Obama's Precision Medicine Initiative, announced in his State of the Union earlier this year, will serve a similar role as the Human Genome Project, moving our understanding of genetics a step further.

As part of the initiative, the president proposed creating a health database of a million Americans. Some see the future opportunity for genome sequencing to pair that health data with genetic information: putting together the genetic suggestions of what could happen in someone's life with what actually happens.

And to really make progress, we need more people to be sequenced.

"You have to compare genomes to learn anything," Lander explained, "maybe between dozens or hundreds or thousands of people with a disease or without a disease."

These efforts are going on across all levels of medicine and research — from individual health systems to industry to countries, like England, focused on collecting genetic information of their citizens.

I opted in to providing my genetic and medical information to the biobank at Green's hospital system, Partners HealthCare, in Boston. This enables them to look at both my genes and my medical records for research purposes.

First, though, I got my own look into my genome.



A glimpse into the future of genome sequencing

10:04 AM ET Thu, 10 Dec 2015 | 02:27

What I learned

I won't pretend that I wasn't nervous when my results came in. This was my last chance to opt out. After \$2,900 and weeks of waiting, I could still choose ignorance.

"Is there anything really bad?" I asked Green and my genetic counselor, Sheila Sutti, on the phone one Friday afternoon in September.

No, they told me. I didn't have any of the things that truly would have changed my outlook on my life. But that didn't mean I had nothing to think about.

I only had one result under "clinically significant findings" in the report

provided by Illumina: I carry one copy of a mutation called Factor V Leiden.

"What it means is that your blood actually clots a little bit faster than people who do not have this mutation," Green told me, in the tone of voice someone uses when they're trying to avoid instilling panic in the person sitting across from them.

How much faster? I thought, instantly mentally chastising myself for all those long plane rides where I never got up and stretched. I could have developed a blood clot and died!

This, according to Green, was a teachable moment.

"Factor V Leiden mutation is a great example of how genome communication can appear worse than it actually is," he said. That's because of the difference between relative and absolute risk.

This mutation makes me six times more likely to have a blood clot than someone who doesn't have it, which sounds pretty scary. But as it happens, an average adult without this mutation has only a 1 in 1,000 risk of getting a blood clot. So my risk is still only 6 in 1,000, or 0.6 percent.

So what do I do with that? As it turns out, the recommendations are pretty similar to what we're all supposed to be doing anyway: maintaining a healthy weight, exercising daily, not smoking and taking walking breaks on long car or plane rides.

"There's a lot of that in genomic information," Green said. "Things we know we should be doing anyway, but we sometimes get some reinforcement."

Looking ahead

But this isn't where my report ended. I also received information about my carrier status, things that wouldn't affect me but could potentially show up if I have kids. They're recessive mutations of which I only have one copy.

And whether they show up in the next Tirrell generation, of course, would also depend on the genetics of my partner: if he also carried any of these mutations, our children would have a 25 percent chance of receiving two copies and having the disease.

I turned out to have three of these recessive variants, for diseases I'd never heard of, but which would be truly devastating. That presents me with the option of having my partner also tested for those to gauge our risk of passing those diseases onto our children, potentially opening up a whole new round of the "do we want to know" questions someday down the line.

An increasing number of hopeful parents are asking themselves those questions, as use of genetic testing in reproductive health booms, according to Cowen's Schenkel. He said about 2 million carrier tests are done each year in the United States and cites a potential market in reproductive health of more than \$3 billion.

Personalizing my medicine

In addition to my genetic signatures for potential disease, my results included a pharmacogenomics report analyzing how my genes indicate I may react to 12 different drugs, from blood thinners like warfarin and Plavix to the cholesterol-lowering medication Zocor.

Many believe this will be among the nearest-term applications of genome sequencing in medicine, using our genetic signatures to improve how we match the right drugs to the right patients.

My genome tells me that I shouldn't take a drug called eltrombopag, for example, which is sold by **Novartis** under the brand name Promacta and increases platelet production. Platelets enable clotting. With my Factor V Leiden mutation, I may not need any extra help with that.

Where do we go from here?

There are still a lot of questions about how useful genome sequencing is for healthy people. Lander, himself a pioneer in the sequencing world, hasn't had his own genome sequenced.

"I don't think the utility right now is mostly for the individual," Lander told me. "The utility is really pushing forward the frontiers of science."

There are exceptions, he explained — if he had cancer, he'd sequence his tumor, "because there are things you could learn that are directly actionable."

And that's predominantly how sequencing is used in medicine today: in targeted areas like cancer, or to aim to end what researchers call diagnostic odysseys — a long search to turn up the source of a mysterious and serious ailment.

Green, my geneticist, is also on the fence about whether healthy people should be sequenced for medical purposes. The findings, he points out, are ambiguous. Mine in particular neither mean I absolutely will have a serious blood clot, nor that I am cleared of worry about other diseases that didn't show up in my results.

And there's always the risk I could overreact. One of my "Variants of Unknown Significance" is a mutation for Lynch syndrome, which predisposes me to certain kinds of cancers, according to my Illumina report. Green disagreed with that finding, telling me he didn't think it was something I should worry about based on his own analysis of the research.

But Green's concern is that I could over-worry, and seek unnecessary tests or medical treatment that could do more harm than good. Or that I'll tell a physician about my Factor V Leiden and he or she will misunderstand the risk and treat me with blood thinners I don't need.

I learned I also shouldn't get too complacent about the things my test didn't reveal. That doesn't mean I won't ever get those diseases; it just means this screen didn't turn them up.

"If you think of whole genome sequencing as a panoramic view that you take on your iPhone, you see the whole horizon; you see different buildings and trees and maybe some people in the background," Sutti, my genetics counselor, explained. "But what if you're trying to zoom in between those trees to find something else? The whole genome sequencing isn't guaranteed to find that little area in between there

unless you zoom up really close and get next to it.”

So if I was really concerned about something in particular, it would still be important to get a specific test, not rely on my whole genome sequencing.

Green also cautioned that while there are federal laws protecting against employers and health insurers discriminating based on genetic information, there are no such protections in place for life insurance, for example.

Still, he anticipates that within eight to 10 years, it will be routine for healthy people to have their genome sequenced, and for that information to be a regular part of every medical encounter. Between now and then, costs are expected to continue to come down, reimbursement by insurers is expected to gain more clarity, and more proof is expected about how useful personal genome sequencing can be.

My book of life

As for me, I did find my thumb drive, what Green refers to as my “book of life.” And as we learn more about genetics, through more and more people getting their genomes sequenced, it will only become more valuable.

When new discoveries are made in genetics, linking certain traits or diseases to different genes, I can delve into my own genome to find out what my personal blueprint tells me. And with Illumina’s svelte iPad app, MyGenome, I can mine my genetic information for even more characteristics about myself than were reported in my clinical analysis.

For example, I can search for a variant linked to green eye color, what I learned was located on chromosome 15. I was surprised to find out I don’t have it. Perhaps my eyes aren’t actually green?

On chromosome 11, I discovered I carry a variant that apparently prevents weight gain from high-fat diets. Note to self: Eat more butter.

So, after all of that, am I glad I did it?

Yes. And I was very happy to learn my results. I can’t say I’ve made any drastic changes to my life as a result of them, but I have started taking walking breaks during longer car rides.

And I know that just because I didn’t turn up with something — a gene predisposing me to early-onset Alzheimer’s disease, for example — that doesn’t mean I’m in the clear. For most of us, genes aren’t our destiny. They’re a blueprint for how we start out, and then life plays a major role.



Meg Tirrell
Reporter
