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23andMe Said He Would Lose His Mind. Ancestry Said the Opposite. Which Was Right?

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In many ways, Matt Fender, a 32-year-old resident of New York City, is the prototypical 23andMe customer: tech-savvy, educated, a bit of a worrier. But he wasn't worried last December when he clicked a button to dump all the raw data from his 23andMe genetic test into a DNA search engine called Promethease, which sorts through data for gene variants that have received a mention in the medical literature.

Mr. Fender didn't expect any revelations. He had already spent $5 on a Promethease report in 2016, which he'd found interesting but not life changing. But the company had recently emailed customers asking them to re-enter their data to be used for future research and quality control. In return, they were offered a free update.

Mr. Fender's update included something new: the terms "PSEN1" and "pathogenic."

Mr. Fender is a coder, not a geneticist, but he had spent enough time scrolling through his 23andMe results to know he had gotten some bad news.

The PSEN1 mutation is associated with an early-onset form of Alzheimer's, and it is often described as "100 percent penetrant," which he quickly came to understand meant no exceptions — everyone with the variant gets the disease. Most show signs by their mid-40s. Mr. Fender, who describes himself as "the kind of guy who gets excited about responsible financial planning," saw all his carefully crafted plans for the future slip away.

The year 2017 was a breakout period for consumer genetic testing. Ancestry.com tested four million people. 23andMe rebounded from being temporarily shut down by the Food and Drug Administration to score a place on Amazon's list of the five top-selling items on Black Friday weekend. One estimate in MIT Technology Review put the number of American adults who now have access to some form of personal genomic data at one in 25.

Genetic health tests are often criticized for providing weak or marginal information about a person's risk for common conditions like heart disease or diabetes. But while many customers get less than they bargained for, some, like Mr. Fender, get quite a bit more.

These reports come plastered with lawyerly admonitions to "consult your doctor." But it's not as easy as that suggests. Most doctors are distrustful of direct-to-consumer testing. They aren't trained — or paid — to go through complicated genetic reports with patients. And they're leery because the information rarely leads to improved treatments.

When Mr. Fender first approached a doctor about his genetic test results, it was 2013, and it was "like he was annoyed at me," Mr. Fender says.

Mr. Fender had purchased the original 23andMe test in part because he had a sister who died of a pulmonary embolism at 23 and he worried about his own risks. The test didn't tell him anything about his chance of having an embolism, but it did say that he carried two copies of a gene variant called ApoE4, which greatly increases one's chance of getting late-onset Alzheimer's disease by age 85.

This information was disturbing but manageable. His doctor wasn't much help, but that limited advice, combined with a lot of online research, led Mr. Fender to look for ways to improve his health through diet, exercise and supplements.

This time, Mr. Fender was prepared for skepticism. His email to his primary care physician was borderline apologetic. "I know this is an area of medicine that is maybe half-baked and possibly annoying to you," he began, before reviewing what he had learned and requesting advice.

"It's not about the issue being half-baked," the doctor replied, "but what the heck do we do about it, once we know, other than create high anxiety?" The doctor referred Mr. Fender to a geneticist, but it turned out he did not see patients under 50 who were not symptomatic and had no family history of the disease.

Mr. Fender then tracked down Jill Goldman, a genetic counselor specializing in dementia at the Taub Institute at Columbia University Medical Center, who described a multistep process of counseling and confirmatory testing that's been the standard of care for 25

years. She typically serves people at high risk of inheriting a disease, and insurance usually covers both the consultations and the tests. But it was unlikely to cover the costs in the absence of family history.

"It was like a chicken-and-egg thing," Mr. Fender observes. "I needed a medical test to prove to them that it was real, but I couldn't get a medical test until I could prove to them that it was real."

Meanwhile, he happened to see a holiday special — $69 — for Ancestry's genetic risk test. He realized he could use it to, in effect, get a second opinion about his PSEN1 variant.

Five weeks later, the results were ready. He downloaded his raw data and returned to Promethease. An hour later, he had a new report. He looked for PSEN1 at the top of the list. It wasn't there.

Dumbfounded, Mr. Fender searched for the variant he was looking for: rs63749911. This time, his genotype was listed as common/normal.

It was good news, and yet, the two tests were at odds. He had heard that both 23andMe and Ancestry were 99.9 percent accurate. Which one should he believe?

"I always think it is important to point out that a 99.9 percent accuracy can still mean errors," Stacey Detweiler, a medical affairs associate at 23andMe, explained via email. "Even if every variant included in our chip was validated for an accuracy of 99.9 percent (which they are not), that still would mean potential for about 600 errors in the 600,000 variants."

In other words, the number of mistakes can be as high as 600 per customer.

Greg Lennon, a co-founder of Promethease, says the company occasionally catches mistakes and warns customers.

Mr. Fender found himself left to grapple with the discordant results on his own. He felt more than ever in need of a doctor's advice.

The direct-to-consumer genetic testing marketplace is a regulatory Wild West. The F.D.A. stopped a proposed deal between Pathway Genomics and Walgreens in 2010 that would have put the tests in drugstores nationwide. It cracked down on 23andMe in 2013, after the company's first major advertising campaign. But these regulatory efforts look like a game of whack-a-mole.

Now the bar is getting lower. A new regulatory structure announced in November by the F.D.A.'s commissioner, Scott Gottlieb, will allow 23andMe and other vetted providers to introduce some tests for health risks without premarket review. This change is expected to usher in a rapid expansion of the consumer genetics industry.

And however limited the rules are for direct-to-consumer genetic testing, they are downright draconian in comparison with the free-for-all world of third-party interpretive services like Promethease, which bills itself as a "literature retrieval system," with no responsibility for the testing or results themselves.

At first Mr. Fender tried to just believe that the Ancestry results were true and that the 23andMe finding was a mistake. It seemed more probable; the PSEN1 variant linked to early-onset Alzheimer's, he learned, is usually inherited, and Mr. Fender's parents are in their 60s and healthy. If he was wrong, he wasn't sure he wanted to know. But he found the lingering doubts disquieting, and eventually persuaded his doctor to order a clinical test of the PSEN1 gene. It was negative.

Mr. Fender, relentlessly upbeat, expresses gratitude for the experience. "It was very motivating," he says, citing how he has improved his diet and learned to cook. It gave him empathy for people suffering from dementia, and he is thinking about developing an app using voice-activated personal assistants like Siri and Alexa.

"People with Alzheimer's lose track of what they are doing and may empty every drawer in the kitchen because they don't remember that they are looking for their keys. Alexa could ask them what they're planning to do and then give them reminders."

He pauses, and it is suddenly easy to imagine what it has been like, spending every day for months picturing a future with dementia. "Like, how's it going looking for your keys, Matt?" he adds.

His story, as bad as it was, could have been much worse. He had both the temperament and the skill to gather crucial information in a relatively short time. A person with fewer resources or different inclinations might have lived for years under that cloud, waiting to get sick.

Mr. Fender's was the first direct-to-consumer surprise that Ms. Goldman encountered but, she acknowledges, it will not be the last. Tens of thousands of people most likely used services like Promethease in 2017, and those numbers are climbing.

"People are going to need help," Ms. Goldman says. "And we are not ready to handle it."