Your Health Is Personal

Why Is This $99 Home DNA Kit Causing Such an Uproar?

23andMe says it can provide you with valuable health information about your genes. The FDA says prove it. What the consumer genetic testing battle means for you.

BY JOSEPH GUINTO

Would you give someone you love a small plastic vial for her birthday and ask her to spit into it?

Rob Abrams did. His wife, Caitlin, couldn't have been happier. She liked it so much she gave Rob the same thing for Christmas. "It was," Caitlin says, "the most nerdy gift I have ever given and received."

The package — a small tube, removable cap, and sealable spit funnel — was a genetic testing kit from California company 23andMe. The Abramses spent $299 on each kit in 2011. Once the couple mailed in their tubes, 23andMe tested their saliva for hundreds of genetic markers. The markers pointed toward clinically useless but nevertheless interesting ancestral information (look, Caitlin had 2.9 percent Neanderthal DNA!). They also pointed toward dozens of potential health risks. By comparing some of the couple's DNA to a database of genetic indicators, the company said it could tell them whether they were at increased risk for a range of diseases, including Alzheimer's disease, breast or prostate cancer, type 2 diabetes, hypertension, heroin addiction, and amyotrophic lateral sclerosis.

And celiac disease, which Caitlin already knew she had. “I was most interested in possible inherited diseases,” she says. “I’d been diagnosed with celiac disease only a year or two prior, and given that my husband and I planned to have children, I thought it might be helpful to see if I was genetically predisposed to it. Since we know that my celiac disease is based in genetics, we felt that we should speak to a doctor about how to avoid exposing our baby to gluten too early and raising his or her risk of presenting the disease at a later date.”

That’s exactly what the Abramses, who live in Santa Fe, New Mexico, did after Caitlin became pregnant last year. And that’s exactly the kind of thing that helped make 23andMe so popular. The company’s Saliva Collection Kit and Personal Genome Service promised consumers direct access to their own genetic data as a first step to helping them delay, diminish, or even prevent development of the kinds of serious medical conditions that might otherwise cause them a lifetime of discomfort or distress.

Its most revolutionary revision: It did so without requiring customers to first visit a healthcare provider. And it worked. As of last year, when the price of 23andMe’s testing kit decreased to just $99, the company had signed up 400,000 customers. (That number has now climbed to about 500,000.) It was also the only company in the market providing health-related genetic testing directly to consumers. As such, it became a media darling. *Time* named the company’s testing kit the “invention of the year.” *Bloomberg Businessweek* said the kit was part of the “next billion-dollar opportunity in healthcare.” And just as 23andMe CEO Anne Wojcicki began making the rounds on *Today* and *CBS This Morning*, *Fast Company* magazine named her “America’s Most Daring CEO.”

One organization that wasn’t applauding: the U.S. Food and Drug Administration. In November 2013, the FDA told the company it had to shut down the service. As of press time in April, you could still take 23andMe’s spit test for $99, but when you receive the results, you’ll only be told about the likely migration patterns of your ancestors. There will be no interpretation about what your genes may mean for your predisposition for celiac disease or Alzheimer’s or cancer or ALS or whether your yet-to-be-conceived child may have blue eyes.

That’s because the FDA has deemed 23andMe’s “nerdy” product to be a medical device that the agency can regulate. It is the FDA’s mission to make sure that medical devices are safe and accurate, and the agency was concerned that 23andMe’s spit test had not been proven to be either. FDA spokeswoman Susan Laine told *Genome* that the agency could not elaborate on its dealings with 23andMe, saying, “We cannot comment or confirm communication between FDA and the company at this time.” But in a letter sent to 23andMe on November 22, 2013, the FDA’s Alberto Gutierrez said 23andMe’s test could raise serious concerns “if test results are not adequately understood by patients or if incorrect test results are reported.”

The FDA has raised concerns about genetic testing for the masses before. In 2010, San Diego-based Pathway Genomics scuttled plans to sell a genetic testing kit in Walgreens stores after the FDA balked. Since then, the company has required customers to have a physician order the test for them. The FDA says its aim is simply to protect consumers from misinformation about their health, or from having access to information they won't fully understand. But others see these moves by the FDA as a rebuke of the current movement toward patient empowerment and the democratization of healthcare — a rebuke that may grow in scope this year. Or, as Nick Gillespie, editor of libertarian website Reason.com, bluntly put it: "When it comes to learning about your own [damn] genes, the FDA doesn't think you can handle the truth."

But the truth about the FDA's actions regarding 23andMe may simply be about protecting consumers. The government has been suggesting for years that something is suspect in the direct-to-consumer genetics information provided by companies like 23andMe. In 2006, the Government Accountability Office, a congressionally funded watchdog, investigated four companies that were testing DNA and offering personalized nutrition. The GAO said it believed all of the companies were misleading consumers by basing their guidance on medically unproven test results. Subsequently, a handful of other government agencies, including the Federal Trade Commission and the FDA, issued warnings to consumers about the reliability of the tests.

The GAO and the FDA are not alone in their concerns. Some medical experts believe the information 23andMe gave consumers was incomplete at best and dangerous at worst. But there are others who believe that giving consumers easier access to genetic information, whether clinically proven or not, will help the long-term health of many individuals and help build a bigger, better database of genetic research. Given the differences of opinion and with 23andMe (as of press time) hamstrung by FDA regulations, it's worth asking: How much information can you now easily obtain about your genetic makeup? And, now that consumers have shown they want to know more about their genes, how will the FDA respond if other entrepreneurs find ways to leverage new technologies that might give consumers that information?

On July 9, 2013, *Us Weekly* breathlessly reported that Angelina Jolie was seen in Hawaii "rocking a plunging neckline." The report, accompanied by photos from the event, went on: "Wearing a low-cut camisole and black pants, Jolie revealed her stunning figure and still-ample cleavage." That an actress once named the "sexiest woman alive" would wear a camisole in Hawaii, much less look attractive in it, would hardly seem like breaking news. But this was the first hint of décolletage Jolie had shown in public since she announced, two months earlier, that she'd undergone a double mastectomy and breast-reconstruction surgery.

That announcement did more than put the paparazzi on alert; it imprinted the names of two genes — BRCA1 and BRCA2 — onto the consciousness of thousands of American women. Commonly pronounced "brak-ah one" and "brak-ah two," these are genes that, when inherited in mutated form, can cause breast or ovarian cancer. According to the National Cancer Institute, about 12 percent of women may develop breast cancer at some point in their life. But 55 to 65 percent of women with the BRCA1 mutation, and 45 percent of women with the BRCA2 mutation, will develop breast cancer by the time they turn 70. Jolie had a mutation in both genes. Genetic counselors told Jolie that her BRCA mutations, combined with her family history, gave her an 87 percent chance of developing breast cancer.

By now, none of those stats is breaking news, either. According to a Harris Interactive/HealthDay poll of 1,100 women conducted just a week after Jolie's photo was snapped by *Us Weekly* in Hawaii, 86 percent had heard of her surgery. Of those, 5 percent said they also planned to consult physicians about whether to have their own double mastectomies or to have their ovaries removed, which Jolie said she also planned to do because of the BRCA mutations. Harris Poll officials say that when you extrapolate that 5 percent of respondents nationwide, it suggests that 6 million women might now be seeking similar advice on ovary or breast removal.

With such a strong public reaction to Jolie's surgeries, it hardly seems coincidental that, in its cease-and-desist letter to 23andMe, the FDA singled out BRCA. "Some of the uses for which [the Personal Genome Service] is intended are particularly concerning, such as assessments for BRCA-related genetic risk," the FDA's Gutierrez wrote. "For instance, if the BRCA-related risk assessment for breast or ovarian cancer reports a false positive, it could lead a patient to undergo prophylactic surgery, chemoprevention, intensive screening, or other morbidity-inducing actions, while a false negative could result in a failure to recognize an actual risk that may exist."

Numerous genetic experts have balked at the notion that individuals can't put the sort of information 23andMe provides in its appropriate context. Among them, Misha Angrist, an assistant professor at the Institute for Genome Sciences & Policy at Duke, has called the FDA's concern that women will seek and obtain potentially unnecessary mastectomies based on 23andMe's test "borderline absurd." And two top experts in the genomics field recently published a joint rebuttal to the FDA's arguments against 23andMe's service. Writing in the journal *Nature,* Robert Green, a genetic researcher at Harvard, and Nita Farahany, a law professor and bioethics expert at Duke, called the FDA's response "unwarranted." Green and Farahany worry that the FDA's actions against 23andMe could "presage similar actions against other consumer health products" like online questionnaires or mobile apps that provide medical guidance based on a user's input, which the FDA has suggested it might also regulate as "medical devices." Still, Green and Farahany do agree with the FDA that 23andMe has yet to validate all of its findings about the health implications found in the genetic variants of its customers, and both also agree that customers

might not fully understand the information they are provided about those implications. But they also believe that "the FDA's precautionary approach may pose a greater threat to consumer health than the harms that it seeks to prevent."

As evidence, they pointed to several studies that suggest inexpensive, direct-to-consumer genetic testing does not create distress in most customers, nor does it push them to get "inappropriate treatment." Among those studies:

- The Scripps Genomic Health Initiative study in 2009 found that in 2,200 people who had their genes tested, "there was no measurable change in anxiety or psychological health" once they had the results.
- The Risk Evaluation and Education for Alzheimer's Disease study, a series of randomized trials funded by the National Institutes of Health from 2000 to 2013, found that even though 40 percent of participants discovered they had an increased risk of developing Alzheimer's, that caused them "only modest and transient distress."
- A Johns Hopkins study in 2010 of three genetics-testing companies found that just over 25 percent of respondents shared their results with their physicians in the months immediately after receiving those results. It also found that less than 1 percent of participants altered their medication as a result of their genetic testing.
- The Impact of Personal Genomics Study funded by the NIH from 2012 to 2013 found that customers of Pathway Genomics and 23andMe were "on average ... briefly less anxious" after getting their results and that their anxiety didn't increase over the 12-month period following the receipt of their results.

Some of those studies align with Caitlin Abrams' experience. She says her test results caused her and her husband "no anxiety whatsoever."

"According to my 23andMe results, I have a slightly elevated risk of multiple sclerosis," she says. "This wasn't too surprising to me given that I already have several risk factors, but the confirmation was helpful. In my case, I mentioned the results to my doctor, who told me that in the absence of symptoms I couldn't be tested. She also pointed out the specific symptoms so I could be aware of them in the future."

That is an ideal outcome for personal genetic testing. A customer takes a test and finds that some of her genes suggest an increased risk for a chronic medical condition. That customer calmly discusses those results with a doctor who advises her there is no immediate risk and tells her what to be aware of in the future.

But some in the healthcare field worry that if personal genetics testing grows unregulated, it will too often lead individuals to insist on expensive and possibly unnecessary testing to confirm or overturn what their genes have supposedly told them. Count Jennifer Gunter, an OB-GYN practicing in both Canada and the United States, among the concerned. Writing on her blog, she says that when presented with the kinds of results 23andMe had been providing, doctors could be vexed as to whether and when to order follow-up testing. "You can get test results that your medical providers just don't know how to manage," Gunter says. "I was always taught that I shouldn't order a test if I have no idea what to do with the result."

Google wants you to know more about your genes. Or, at least, one of the founders of the search-engine giant seems to have wanted that. 23andMe was founded in 2006, backed with funding from Google. The company's CEO was (and still is) Anne Wojcicki, the now-estranged wife of Google co-founder Sergey Brin. Brin is also a 23andMe user. Through the company's testing in 2008, Brin discovered he had a mutation in a gene called LRRK2, putting him at elevated risk of developing Parkinson's — a disease his mother already has. Since then, Brin has been on an exercise and nutrition plan, hoping to slow down or stop the onset of the disease. He has also donated more than $130 million to Parkinson's research.

Brin and Wojcicki gladly began telling that story four years ago — to *Marie Claire*, to *Bloomberg*, and to *Wired* magazine, which ran a lengthy profile on the notoriously press-shy Brin in July 2010. That same month, the GAO came out with a report about consumer-level genetics-testing companies.

In the GAO investigation, five volunteers purchased 10 tests from four companies, including 23andMe. Each volunteer got highly conflicting results from the tests. One was told that he was both at below-average and above-average risk for prostate cancer and hypertension. Others received disease predictions that were at odds with their actual medical conditions. Testifying before the U.S. House Subcommittee on Oversight and Investigations, Gregory Kutz, a GAO investigator, concluded, "The test results we received are misleading and of little or no practical use to consumers."

You don't have to look hard to find genetic experts who more or less agree about the practicalities of direct-to-consumer genetic testing, even if they support the right of consumers to have those tests available. At one recent Harvard Medical conference for personalized medicine — which was overrun with doctors and researchers in favor of genetic/genomic testing — the test was called "entertainment" to distinguish it from something with clinical utility. Even those with a 23andMe association are cautious. Michael Eisen, a biologist at the University of California at Berkeley who is also on the scientific advisory panel for 23andMe, recently wrote the following on his personal blog: "Looking at your own DNA is really interesting, but it only rarely provides actionable new

information. We have an incomplete catalog of human genetic variation. ... In many cases current, incomplete, data may point to someone having an elevated risk of some disease, when they really have a lower than average risk. ... The data are, at this point in time, very, very messy."

Besides, Eisen points out, 23andMe's tests only provide "SNP genotyping, not whole genome sequencing." That means the 23andMe test identifies genetic markers known as single nucleotide polymorphisms, often referred to as SNPs (called "snips"). SNPs are positions along the DNA chain where people commonly differ from one another. 23andMe's test measures 1 million of these, but there are many other types of genetic variants that aren't measured by these tests. As Robert Klitzman, who heads the master's of bioethics program at Columbia, put it in a recent *Bloomberg* opinion piece, "The problem with these test kits is scientific. Only part of a person's DNA is tested, and scientists are still unsure how to interpret most of the information. ... The test from 23andMe misses many genes that may be involved in a disease."

The FDA has long agreed. In June 2010, the agency informed five direct-to-consumer genetics-testing companies that it intended to regulate their products as medical devices, which would require the companies to prove the products performed as advertised. By May 2013, as Jolie was announcing her BRCA mutations, the only one of those companies still in the business of selling health-related testing kits directly to consumers was 23andMe. But that same month, the company stopped communicating with the FDA about how it intended to prove its product was accurately matching DNA samples with increased or decreased likelihood of acquiring certain diseases. Six months of silence later, in November 2013, the FDA told the company to stop marketing and providing the health-related aspects of its genetic tests. Care to guess whom *Fast Company* magazine lauded on its cover that same month? Right. Wojcicki. *Forbes*, however, had a slightly different take, headlining a story about the FDA's November 22 action to stop 23andMe's tests as "23andStupid." Wrote *Forbes*' Matthew Herper, "This is not the story of a big regulator choosing to squash a small company, but of a company that decided that it didn't have to follow the rules."

But consumers don't always have to follow the FDA's rules. In addition to a report on your likely ancestry, if you order a 23andMe spit kit today, you will receive raw genetic data that has not been spun through the company's database to match your genetic markers with the potential for developing diseases, or with the ability to smell asparagus in your own urine (which, yes, was part of the test). But you could take that raw data to an outfit like Promethease. Developed in 2006 by programmer Mike Cariaso, Promethease is software that does gene-to-disease matching similar to that which 23andMe offered.

Cariaso's Promethease programming partner Greg Lennon says Promethease "is basically just a report consisting of the links between a given set of DNA variations and the literature about them. The basic Promethease program was — and remains — free for any individual to use."

But for $5, anyone with raw data from 23andMe can run that data through Promethease and get a report that would still tell them if, for example, they are at elevated risk for Alzheimer's. Not that this is advisable, but in an age when too many people turn to the internet for medical direction, it does happen.

In other words, the Pandora's box of direct-to-consumer genetic testing remains open. For now, anyway. Cariaso told *Genome* he hasn't heard from the FDA yet. "We're hoping to be left out of this kerfuffle," he says. "But we're probably open to making changes if requested."

Still, he doesn't agree with the FDA's contention that direct-to-consumer testing will cause customer concern and confusion. "Given a large enough sample, certainly somebody will overreact," Cariaso says. "The same is true of a bathroom scale or a thermometer. But I think there is a much greater opportunity for this information to do good than harm. No doctor is going to perform surgery based on a 23andMe report without follow-up testing."

And for Gholson Lyon, assistant professor in human genetics at Cold Spring Harbor Laboratory on Long Island, that's just the point. He agrees that genetic data on its own may not be a foolproof measure of the potential for us to develop certain diseases or a guarantee that we *won't* develop certain diseases. But the follow-up information, the doctor visits, the testing, and the building of a national or worldwide genetic database that could result, is worthwhile. "Information is power, and this information is helping people learn more about their health and leading them to talk with their physicians," he says. "Somehow the U.S. government finds it acceptable to store massive amounts of data about its own citizens and those of the rest of the world. But if the same people want to spend their own money to advance genomic medicine and possibly improve their own health in the process, they want to stop them."

For their part, FDA officials have said they support individuals' rights to access their own DNA data. "We just have concerns with how it's being interpreted," the FDA's Gutierrez recently told *Bloomberg Businessweek*.

And until 23andMe can prove that the science behind its interpretations is sound, you'll have to look elsewhere for information on what your genetic makeup might mean for your health. Whether or not that information is accurate and useful, for now, remains a matter of debate.