23andMe: The Business and Ethics of Personal Genetics Testing

In late November 2013, CEO Ann Wojcicki and her leadership team at 23andMe received a sternly worded letter from the U.S. Food and Drug Administration (FDA). The FDA stated that the company’s marketing of a genetic test and follow-on display of disease predispositions violated the law. The FDA letter posed an existential threat to 23andMe’s business and appeared to validate concerns in the medical community that the company was misinforming the public.

Nevertheless, people worldwide wanted to learn about their individual disease risk. Preventive medicine was gaining traction and was supported by the 2010 Affordable Care Act. 23andMe’s links to San Francisco-based social networking companies and leading-edge biotechnology firms positioned it strongly relative to competitors. Furthermore, the company had just secured two important patents. The first covered a method to identify genetic variants associated with susceptibility for Parkinson’s disease. More controversially, the second patent was for gamete donor selection during in vitro fertilization, decried by bioethicists as enabling “designer babies.”

The FDA’s action was immediately criticized in some quarters as outdated protection of physician control over medical decisions. Since adding new customers was critical to the expansion of datasets that 23andMe planned to use to democratize biomedical research, Wojcicki and her team faced a dilemma. The company could pause to sponsor rigorous clinical trials in support of a formal application to the FDA, but that would take years and methods for test validation were not yet standardized. Alternatively, 23andMe could test only for family lineage and supposedly inherited behavioral traits, but that was likely to restrict the company’s growth.

From the Human Genome Project to Personalized Genetic Testing

Starting in 1990, the U.S. Department of Energy and the National Institutes of Health jointly sponsored a massive project to map the three billion base pairs that make up the human genome (which consists of approximately 20,500 genes). At a final cost of $3 billion, the Human Genome Project was completed in 2003 thanks to major advances in DNA sequencing methods and instrumentation. Despite the hopes of early advocates, the project generated few findings that could be translated immediately into new medicines.

A key finding from the project revealed that 99 percent of DNA sequences are identical among humans. But variations that occur every 100 to 300 base pairs along the genome drew attention. These single-point mutations, also called single nucleotide polymorphisms (SNPs, or “snips”), offered genetic markers that could be identified using relatively inexpensive tests. As large genomic databases became available, tests were developed to
draw statistical correlations between SNPs and inherited diseases such as Alzheimer’s, dietary conditions such as celiac disease, and responses to medicines such as the blood thinner warfarin. In addition, SNPs could be used to map familial genetic relationships and even geographic migrations of population subgroups.

Personal Genetic Testing Comes to Market

In the mid-2000s, several companies began to offer genetic testing directly to the public. It was no longer necessary to get a physician’s prescription for a test and have results held and reviewed by a doctor. Now consumers could order a test online and pay by credit card. Typically, a sample collection kit was delivered to a consumer through the mail (see Exhibit 1). The consumer then spit saliva into a modified test tube and sent it back to the company’s labs using pre-printed mailing labels. Next, the company processed and analyzed the sample, using microarray technology to identify SNPs in the DNA. SNPs were compared to the occurrence rates of various health conditions within the customer’s gender, ethnicity and age group to determine their risk profile for diseases, likely response to certain medicines, and paternal and maternal lineage. Within 30 days, test results were available online through the company’s password-secured portal. By 2007, 26 companies offered genetic test services, though they differed in the number of gene variants analyzed and how they presented information on disease risk, dietary conditions, and familial lineage to customers.

Founded in 2006, 23andMe would prove to be one of the few firms that sustained its vision for direct-to-consumer (DTC) genetic testing as most of its competitors changed business plans or exited the sector. To launch, Wojcicki raised $8.9 million in funds from Google, Genentech, several venture capital firms, and her husband Sergey Brin, one of the original founders of Google. Wojcicki had grown up in the Silicon Valley with personal ties to numerous high-tech company founders. After earning a B.A. in Biology at Yale, she worked for a decade at the Wall Street firms Investor AB and Passport Capital. When Brin and Larry Page started their search engine company, they rented the garage of Wojcicki’s sister.

Sales of a test kit started in 2007, priced at $999 for reports covering 14 conditions and sensitivity to several prescription drugs. By 2009, the price had been lowered to $399 for ancestry analysis, $429 for health analysis now encompassing 150 conditions, or $499 for a combined analysis, plus $7 monthly for ongoing access to the company’s membership-only site. The price dropped further the following year to $299 for a suite of 244 conditions and sensitivity to 18 medicines. Monthly subscription fees were phased out in 2011.

Customers who purchased the 23andMe test received gene-disease associations along with a host of genealogical data, links to published scientific articles, and access to discussion forums. Reports of risk for a given disease specified a percent chance of getting the disease over a lifetime (see Exhibits 2 through 4). Beyond an association between gene and phenotype as typically reported in scientific papers, 23andMe had developed algorithms that calculated the probability of a specific disease for a specific customer based on the
population-wide prevalence of a disease, an estimate of the importance of each genetic variant, and personal information supplied by customers and stored in a profile.

Critical Responses and Consumer Uptake

Almost immediately, scientific critics questioned the statistical and medical associations drawn by 23andMe between gene variants and diseases, and criticized the associated disease prevention advice available from the company or through other online searches. While nearly all of the DTC genetic testing providers had disclaimers on their websites recommending that customers discuss results with medical experts, surveys suggested that few people did so. A study of test users carried out in 2010 found that only 10 percent consulted a genetic counselor and just 25 percent shared their results with a physician.\(^5\)

Shortly after 23andMe’s launch, the American Society for Human Genetics issued a statement regarding DTC genetic testing: “In the current environment, consumers are at risk of harm from DTC testing if testing is performed by laboratories that are not of high quality, if tests lack adequate analytic or clinical validity, if claims made about tests are false or misleading, and if inadequate information and counseling are provided to permit the consumer to make an informed decision about whether testing is appropriate and about what actions to take on the basis of test results.”\(^6\)

Francis Collins, leader of the Human Genome Initiative and director of the U.S. National Institutes of Health was more blunt: “Just because we have identified a gene doesn’t mean its function or its impact has been thoroughly understood or that having a gene has any real predictive value.”\(^7\)

Yet, within a year of its market introduction, Time magazine named 23andMe’s test kit the “innovation of the year.” A laudatory article suggested: “We are at the beginning of a personal-genomics revolution that will transform not only how we take care of ourselves but also what we mean by personal information. In the past, only elite researchers had access to their genetic fingerprints, but now personal genotyping is available to anyone who orders the service online and mails in a spit sample. Not everything about how this information will be used is clear yet … but the curtain has been pulled back, and it can never be closed again.”\(^8\)

For Wojcicki and Brin, use of 23andMe’s test kits also had a personal dimension. According to a profile in Vanity Fair: “Brin’s great-aunt suffered from Parkinson’s, and his mother was diagnosed with it in 1999. When Wojcicki tested Brin, his results were positive for the mutation. Brin read the risk as possibly having only about 10 good years left.”\(^9\) Wojcicki also spoke often about her own test results, which revealed an elevated risk for breast cancer and that she was a carrier for Bloom’s syndrome, an inherited disorder characterized by short stature, sun-sensitive skin changes, an increased risk of cancer, and other health problems.\(^10\)
Targeting One Million Users

A new price plan and corporate reorganization were announced in December 2012 with the infusion of an additional $50 million from a second round of venture fund investments. Money came from Brin, Google, Google Ventures, several other venture funds and the Russian billionaire Yuri Milner, known for investing in high-tech startups including Facebook. The price for test kits, which now covered 254 diseases and medical conditions, was lowered to $99. Wojcicki began an active campaign to get one million members in order to increase the company’s database and intensify health research.

Advertisements were placed on social media sites, in on-line magazines, and the company even paid for a blimp to carry ads in the San Francisco region. Additional press attention came when movie star Angelina Jolie had a double mastectomy in May 2013 upon discovering that she carried a version of the BRCA gene that raised her risk for breast and ovarian cancer. A series of television and YouTube commercials were launched in August 2013, emphasizing the lower price and opportunities for consumers to empower themselves with information about their unique disease risks.

According to Wojcicki, an increase in the customer base would lead to a transformative moment in the history of medicine: “One million customers can be the tipping point that moves medicine into the molecular era... A genetic data resource of this magnitude has enormous potential to address unanswered questions related to the contributions of genes, the environment and your health... [This is] an ambitious plan that could transform medicine for generations to come.”

Research using 23andMe’s Data

23andMe invited purchasers of its testing services to join a community of like-minded people and even to initiate research projects with fellow test-takers. The company routinely asked customers to complete surveys concerning diet, lifestyle, and family histories. Studies then identified genetic associations in areas ranging from food allergies to life-threatening diseases. For example, scientists at 23anMe collaborated with researchers at the U.K. University of Bristol on a publication in Nature Genetics that identified allergy susceptibility loci.

The company especially touted its efforts to genotype over 10,000 people with Parkinson’s and had published research that identified two new genetic associations for the elusive disease. Researchers at 23andMe also found that Parkinson’s disease was associated with back pain and the need for joint replacement surgery; in another study, they found that patients with Parkinson’s had better than average metabolic health.

Yet scientists experienced with the potential fallacies of correlational studies between genes and disease worried that 23andMe was raising false hopes of certainty and simplistic genetic
answers for complex ailments. Studies linking ancestral origin, alcohol consumption, and “whether you are an extravert,” for example, appeared dubious or outright misleading.\textsuperscript{16}

Also of concern to some users and bioethicists, 23andMe began to license consumers’ data to pharmaceutical companies. A partnership with Genentech to research the genetics of Alzheimer’s disease was announced in mid-2011. Participation was voluntary, and those who shared data and completed questionnaires were eligible for up to $100 in compensation.\textsuperscript{17} A second study was initiated with Genentech in 2012; it sought to identify genetic variants associated with long-term cancer remission in patients who had previously taken the Genentech drug Avastin (bevacizumab).\textsuperscript{18} Neither company disclosed financial arrangements underpinning the research projects.

It its consent forms, 23andMe described safeguards governing how it held and made use of genetic data. By answering surveys and customized questions, consumers were providing consent to data uses by “23andWe,” the research arm of 23andMe: “The 23andWe study is open-ended: new surveys and features may be added to 23andWe on a continuing basis. … Your participation in this research project is completely voluntary.”\textsuperscript{19}

Even if customers chose not to answer surveys, their data still could be used for research and commercial purposes. The company required test kit purchasers to agree: “If you do not give your consent to participate in 23andWe Research, 23andMe may still use your genetic and self-reported Information for purposes such as quality control or other R&D activities. Genetic and self-reported information used for such purposes may be included in aggregated genetic and self-reported information disclosed to third-party research partners who will not publish the information in a peer-reviewed scientific journal. Research partners may include commercial or non-profit organizations that conduct or support scientific/medical research or conduct or support the development of drugs or devices to diagnose, predict, or treat health conditions.”\textsuperscript{20} Some customers were upset when the company obtained a patent on a method for determining predisposition to Parkinson’s disease, arguing that disclosure was not the same as informed consent to the use of their genetic information.\textsuperscript{21}

**Regulatory Interventions**

In March 2009, a report by the Government Accountability Office found inconsistencies in disease risk as reported by several DTC genetic testing companies and wide variation in laboratory results. A follow-up study in 2010 expressed concerns about the potential to mislead consumers, especially since the companies offering the services used different methods to calculate risk profiles for diseases.\textsuperscript{22}

At the same time, a few bioethicists noted gaps in the 2008 Genetic Information Privacy Act (GINA). The act protected individuals from employer or health insurance discrimination based on their genetic data; it also put stricter rules in place governing how health providers used patient records or referenced patients undergoing care.\textsuperscript{23} But GINA did not explicitly...
protect Americans from selective use of genetic data by life insurance providers or when seeking disability or long-term care coverage. Other misuses or exploitation of genetic data were easy to envision, ranging from unwarranted behavioral interventions in children to surveillance of adults with particular genotypes.\textsuperscript{24}

Congressional leaders picked up on the concerns, including Henry Waxman (D-CA), who in 2010 organized hearings in the powerful House Committee on Energy and Commerce. Opening the hearings, Waxman warned: “The science informs us that there is no widely accepted consensus linking genetic markers to specific illnesses.”\textsuperscript{25}

At the hearings, the CEO of 23andMe’s main domestic competitor, Navigenics, pledged cooperation with regulators and the medical establishment. Navigenics had already shifted from a DTC model to requiring that tests be ordered by a physician or corporate wellness program.\textsuperscript{26} Vance Vanier, the CEO, noted: “We firmly believe that a healthcare professional should be an integral part of the personal genetic analysis process ... We are dedicated to maintaining the privacy and security of all of our customers’ genetic information, never selling or sharing individuals’ personal genetic information with third parties.”\textsuperscript{27}

By contrast, 23andMe’s spokesperson to Congress, general counsel Ashley Gould, envisioned DTC tests as a disruptive force in medicine. She began by stating: “Customers have a fundamental right to access their personal genetic information ... 23andMe provides a platform for customers to participate in the research process, so that we can all learn more about genetics and diseases.” Gould also explained the disease risk associations that 23andMe presented to customers as built on “established research” and “associations based on preliminary research” so that “our customers know the most current information about what their genome says.” Turning to the potential for FDA regulation, Gould drew an analogy between DTC genetic tests and over-the-counter tests for HIV, hepatitis, cholesterol, and pregnancy: “Although the results of the FDA-approved, over-the-counter tests may lead to customers receiving potentially distressing information, the FDA has permitted consumers to have direct access to these tests.” Gould concluded that regulation of 23andMe’s services would stifle innovation and explained: “We have been working on a proposed framework that we will present to the FDA tomorrow.”\textsuperscript{28}

Speaking on behalf of the FDA, Dr. Jeffrey Shuren, director of the Center for Devices and Radiological Health, warned of inaccuracies in tests and unproven links between SNPs and clinical outcomes. Shuren stated: “Failure to validate the accuracy, reliability, and clinical implications of a test can result in patient harm from misdiagnosis, failure to treat, delay in treatment, inappropriate treatment, or avoidable adverse events.” He next explained that FDA oversight of medical devices extended to tests that diagnosed disease or were intended to cure, treat, or prevent disease. By contrast, tests to determine ancestry were not considered devices under the law. Focusing on DTC genetic tests, Shuren provided a laundry list of problems the FDA had encountered, ranging from faulty data analysis to unacceptable clinical performance. Referencing letters sent to DTC genetic testing companies, including 23andMe, Shuren explained their products and services met the
"statutory definition of a medical device on the basis of the manufacturers’ claims about the test results." Interestingly, he also addressed the issue of innovation, warning: “the ability of laboratories to market tests without any regulatory oversight creates a disincentive for traditional manufacturers to develop new tests, thereby stifling innovation.”

A year later, the FDA convened an advisory panel to examine DTC genetic tests. Guest speakers, ranging from leading scientists to academics and lawyers, presented updates on the state of research using SNPs and ethical and policy concerns related to genetic tests. For example, Nancy Wexler, president of the Hereditary Disease Foundation and a professor of Neuropsychology at Columbia University, drew on research into Huntington’s Disease to warn that predictive testing for genetic diseases can harm people who receive a devastating diagnosis. Panel members discussed risks and benefits of making clinical genetic tests available for direct access without the involvement of a clinician; ways to mitigate incorrect, misinterpreted, or miscommunicated DTC genetic test results; and how to determine that genetic tests are safe and effective. Discussion tilted toward limiting test use, communicating results through medical professionals, and mandating strict standards for tests.

Shortly after the March 2011 meeting, the FDA sent letters to DTC companies requesting they submit their products and services for pre-market review. Specifically, the agency informed firms that their DTC genetic tests were “devices” under the law. Unlike an in vitro test, which had to meet only standards for labeling and quality control prior to marketing, a device had to be proven safe and effective through controlled clinical studies, or proven equivalent to an existing approved device.

23andMe was in contact with the FDA throughout the sequence of government studies, Congressional hearings, and FDA advisory committee meetings. In 2011 and 2012, the company and the agency went back and forth on categorizing DTC testing. 23andMe argued DTC genetic tests should count as class II medical devices, analogous to in vitro testing, and thus requiring analytical validation through documented experiments. The FDA, however, consistently held that 23andMe’s tests were a class III device because of the potential for risk of injury from a false test result. A class III device required clinical validation through formal trials in addition to analytical validation.

On November 22, 2013, the FDA sent Wojcicki an official “warning letter” that stated: “23andMe must immediately discontinue marketing the PGS [personal genome service] until such time as it receives FDA marketing authorization for the device.” The letter explained that 23andMe’s DTC genetic tests were a device under the law since they provided health reports on 254 diseases and conditions. Citing the BRCA breast cancer assessments as an example, FDA officials were concerned with the possibility of “health consequences that could result from false positive or false negative assessments for high-risk indications.” The agency also warned: “false genotypes for your warfarin drug response test could have significant unreasonable risk of illness, injury, or death to the patient.”
The FDA appeared frustrated by the company’s failure to take its regulatory authority seriously: “As part of our interactions with you, including more than 14 face-to-face and teleconference meetings, hundreds of email exchanges, and dozens of written communications, we provided you with specific feedback on study protocols and clinical and analytical validation requirements, discussed potential classifications and regulatory pathways (including reasonable submission timelines), provided statistical advice, and discussed potential risk mitigation strategies … However, even after these many interactions with 23andMe, we still do not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses, which have expanded from the uses that the firm identified in its submissions.” 23andMe’s new marketing campaigns, which included online and television commercials, suggested to the agency that the company was expanding DTC test offerings without any consideration of the FDA’s regulatory authority.

Five days after the FDA’s regulatory letter, a class action lawsuit was filed in California, alleging that: “23andMe, Inc. falsely and misleadingly advertises their Saliva Collection Kit/Personal Genome Service (‘PGS’) as providing ‘health reports on 240+ conditions and traits, drug response, carrier status,’ among other things, when there is no analytical or clinical validation for the PGS.” The suit warned also that information generated about consumers was marketed to other firms, “even though the test results are meaningless.”

Consumers, Customers, and Experts

Customers of 23andMe were typically young with interests ranging from disease prevention to seeking information on family history, including geographic ancestry and ethnicity. Research studies of early adopters of DTC genetic tests found they did not suffer either major negative or positive effects in terms of nihilism, depression, or changes to diet and behaviors. Early users also appeared to treat the findings with nuance rather than adopting fully genetic determinist views.

Those seeking to learn more about their familial ancestry had fewer reasons to worry about disease risk percentages presented by 23andMe. But ethicists and regulators had concerns about the impact people’s self-perception when results contrasted sharply with existing ethnic identities. People who self-identified as African American or partially Native American were not always prepared for test results revealing European or other ancestry.

Advice columnists saw the results. For example, a letter writer to the “Dear Prudence” column in the Washington Post worried: “I recently got my genetic profile done by 23andMe, and was a bit shocked to discover I had no Native American blood. I’m just a plain old 100-percent European mutt. My entire life my mother has prided herself that she had Native American heritage from her grandmother, and I’m trying to decide whether to broach the subject with her that it’s just not true.” The advice columnist recommended dropping the issue: “The result is convincing enough for you to accept none of your ancestors crossed that Bering Strait ice bridge. But I bet you could show your mother enough STRs and SNPs from
your shared DNA to fill a teepee, and nothing would persuade her that her grandmother wasn’t part Cherokee.”

Physicians, biomedical research scientists, and medical ethicists largely supported the FDA’s intervention. For example, in a column in the *Annals of Internal Medicine*, the geneticist and physician Michael Murray noted: “The health system is unprepared to handle these PGS [personalized genome service] reports. Some persons have proposed that clinician education is a solution. However, although it is true that clinicians need genomics education and that physicians often do not know as much about genomics as the educated consumers who are presenting them with these reports, lack of education is not the core problem. The core problem is a lack of evidence.”

Responding to the FDA and critics, Wojcicki remained focused to open access to health information as the best way to develop new cures and motivate disease prevention. Interviewed by the *New York Times*, she noted: “I remember in the early days of Google, Larry would say, ‘I just want the world’s data on my laptop.’ I feel the same way about health care. I want the world’s data accessible.” In her vision, 23andMe could speed the slow pace of government-funded biomedical research. Wojcicki argued: “Genetics is going to be a ubiquitous part of health care. I think that everyone is going to get their genome. At some point, health care is going to reimburse for it. And you’re going to hear stories of people really taking ownership of health prevention, directed by their genome.”

Some geneticists and public commentators criticized the FDA’s logic behind regulating the 23andMe test. Thus Misha Angrist, an assistant professor at the Duke Institute for Genome Sciences and Policy, argued it was “borderline absurd” for the FDA to suggest that women would get a mastectomy based on the 23andMe test. Likewise, the libertarian Ronald Bailey wrote: “What the test results would actually lead patients to do is get another test and talk with their physicians.” Bailey also observed: “It is notable that the FDA cites not one example of a patient being harmed through the use of 23andMe’s genotype screening test.”

Market analysts nevertheless were skeptical of Wojcicki’s approach. A commentator for *Forbes*, which routinely criticized the FDA as overly bureaucratic and anti-innovation, noted: “outside of a crowd of libertarians and genoscenti, the company does not have the political support it needs for a fight against the FDA. And none of its high-minded ideals release it from the requirement the FDA wants to enforce: that a medical device has to work.”

**An Uncertain Future**

In the wake of the FDA announcement, 23andMe revamped its website and advertisements to solely describe itself as “the largest DNA ancestry service in the world.” With no explicit mention of disease risk, the company instead marketed the opportunity for users to search and explore genes contributing to traits such as lactose intolerance, athletic ability, and food preferences; compare their profiles to family and friends; and discover their genetic roots by
gaining insights into their ancestry and genealogy (see Exhibit 5). Other changes in early April 2014 included hiring business managers and lawyers with decades of experience in the biotechnology sector into newly created regulatory affairs and business development positions. Nevertheless, Wojcicki continued to speak publicly of her plans to empower individuals to learn of their personal genetic risk factors and take action. 23andMe, she announced in March 2014, had over 650,000 customers in its database.\textsuperscript{44}

For 23andMe, the source of proof of the predictive utility of personal genetic tests remained unclear. Was the right next step for 23andMe to raise funds for structured clinical trials that could take years or decades to generate definitive results? Or should the company wait for the scientific community to reach a clearer consensus on the utility of SNP variations?

For the FDA, growth of personal genetics testing posed a regulatory dilemma. The agency was being accused of holding back a new era of medical progress. The costs to sequence human genomes was dropping exponentially (see Exhibit 6), creating the appearance of an agency that was behind the science instead of on the leading edge. Should the FDA limit DTC testing to family genetics and historical lineage? Or should it be more open to a future in which consumers had personalized estimates of disease risks? Would the tests support efforts by physicians and public health officials to get people to eat healthier and exercise more? Or would tests undermine medical authority and harm individuals and communities? Did people have a right to not learn of their disease risks?

The FDA warning letter to 23andMe had sent a signal to the industry more generally. Yet, as the cost of testing dropped further, many physicians, geneticists, and others expected that entire genomes would be sequenced and linked to patients’ electronic health records. Under the 2010 Patient Protection and Affordable Care Act, government funds were available to support the creation of large databases that could incorporate genetic data. But it remained unclear how to strike a balance between on the one hand, concerns of privacy and the protection of personal genetic information, and on the other hand, enabling novel biomedical research.
Exhibit 1. 23andMe Test Kit

Source: http://bionicly.com/2012/12/23andme-review, reproduced with permission of Stephen Davies.

Exhibit 2. 23andMe Test Results: Health Overview

Source: http://bionicly.com/2012/12/23andme-review, reproduced with permission of Stephen Davies.
Exhibit 3. 23andMe Test Results: Disease Risk

Source: http://bionicly.com/2012/12/23andme-review, reproduced with permission of Stephen Davies.

Exhibit 4. 23andMe Test Results: Predicted Pharmaceutical Therapy Response

Source: http://bionicly.com/2012/12/23andme-review, reproduced with permission of Stephen Davies.
Exhibit 5. 23andMe Test Results: Lineage

Maternal Haplogroup: H39

Maternal Haplogroup: H39

H39 is a subgroup of H, which is described below.

Locations of haplogroup H circa 500 years ago, before the era of intercontinental travel.

H originated in the Near East and then expanded after the peak of the Ice Age into Europe, where it is the most prevalent haplogroup today. It is present in about half of the Scandinavian population and is also common along the continent's Atlantic coast.

Source: http://bionicly.com/2012/12/23andme-review, reproduced with permission of Stephen Davies.

Exhibit 6. Cost to sequence a complete human genome

Notes


26 Life Technologies, a medical device and diagnostics company, acquired Navigenics in 2012. Consumers’ genetic data was available on a password controlled website through August 2015, after which it was scheduled to be deleted.


34 Casey v 23andMe, Inc., U.S. District Court for the Southern District of California, Case 13cv2847-JAH-JMA.


