



23andMe and the FDA

George J. Annas, J.D., M.P.H., and Sherman Elias, M.D.

In August 2013, the genetic-testing company 23andMe began running a compelling national television commercial, in which attractive young people said that for \$99 you could learn “hundreds

of things about your health,” including that you “might have an increased risk of heart disease, arthritis, gallstones, [or] hemochromatosis” (www.ispot.tv/ad/7qoF/23-and-me). It was the centerpiece of the company’s campaign to sign up 1 million consumers. On November 22, the Food and Drug Administration (FDA) sent 23andMe a warning letter ordering it to “immediately discontinue marketing the PGS [Saliva Collection Kit and Personal Genome Service] until such time as it receives FDA marketing authorization for the device.” On December 5, the company announced that it was complying with the FDA’s demands and discontinued running the commercial, noting on its website, “At

this time, we have suspended our health-related genetic tests to comply immediately with the [FDA] directive to discontinue new consumer access during our regulatory review process.”

23andMe’s services relied on single-nucleotide polymorphism (SNP) technology to identify genetic markers associated with 254 specific diseases and conditions (the list has grown over time), which, the company said, could inform people about their health and how to take steps to improve it. In the words of 23andMe’s TV commercial, “Change what you can, manage what you can’t.” In its warning letter, the FDA said it was concerned that 23andMe failed to supply any indication that it had “analytically or clini-

cally validated the PGS for its intended uses.” The agency was also concerned about how consumers might use information concerning breast-cancer mutations and warfarin-related genotype results. The company and the FDA had been in continuous negotiations since July 2009, but in May 2013, the company stopped communicating with the agency. The company’s failure to attempt to resolve the issues identified by the FDA, while it continued marketing the product, led to the warning letter. The FDA has not yet developed specific rules for direct-to-consumer (DTC) genetic testing, and whether government regulation or private litigation will determine the future contours of DTC genomic sequencing will probably depend on the extent to which consumers and physicians support government regulation.^{1,2}

23andMe had previously framed DTC genetic testing as consumer

23andMe CONSENT

23andMe, a leading DTC genetic testing company, informs its customers that they might receive unexpected information in their results. In its “Terms of Service,” 23andMe alerts its customers, before purchase, that a resulting finding “may evoke strong emotions and has the potential to alter your life and worldview. You may discover things about yourself that trouble you and that you may not have the ability to control or change (e.g., your father is not genetically your father, surprising facts related to your ancestry, or that someone with your genotype may have a higher than average chance of developing a specific condition or disease). These outcomes could have social, legal, or economic implications.”

In addition, customers must opt in to view particularly sensitive information in “locked reports” that are not initially displayed on their results page.

Locked Reports ?				
NAME	CONFIDENCE	YOUR RISK	AVG. RISK	COMPARED TO AVERAGE
Alzheimer's Disease update	★★★★	🔒	🔒	🔒
Parkinson's Disease	★★★★	🔒	🔒	🔒

Before selecting a “locked report,” customers are provided with additional information about the nature of the information without seeing their individual results.

Your results do not affect whether you see the text below. Everyone must view this information before choosing whether to view their results for this report.

Parkinson's Disease is a serious disease with no known cure for which strong genetic factors have been established. Consider the following before choosing whether to view your genetic data regarding Parkinson's Disease:

- **Genetics can substantially affect your Parkinson's risk:** This report includes information on a relatively rare mutation in the LRRK2 gene associated with significantly increased risk in European populations, in addition to other variants with relatively smaller effects in both European and Asian populations.
- **Your family history affects your chances of having the LRRK2 mutation:** Though rare in the general populations, this mutation is much more common in families with European ancestry and a history of Parkinson's.
- **These genetic variants cannot predict definitively whether you will develop Parkinson's:** Genes and environment both contribute to a person's chances of developing Parkinson's. Many people who have the risk-associated versions of the genetic variants in this report will never get the disease. Conversely, lacking these versions does not substantially reduce one's Parkinson's risk below average.
- **This information may have implications for your relatives:** Because you are genetically similar to your relatives, anything you learn about your own genes may have implications for them as well.
- **The significance of your genetic information could change:** The development of new treatments or cures could substantially change the implications of this information. New discoveries could refine our understanding of the risks associated with certain genotypes or link them to additional diseases or conditions.

[I understand, please show me my results](#)

From the Presidential Commission for the Study of Bioethical Issues.⁴

empowerment — giving people direct access to their genetic information without requiring them to go through a physician or genetic counselor. To oversimplify, the debate has been framed as a struggle between medical (or government) paternalism and individuals' right to information about ourselves. In this sense, it is not so different from the older debate about whether patients should have direct access to their

medical records and test results, which was ultimately resolved in favor of direct patient access. We think the day will come when this framing is appropriate, but not until the diagnostic and prognostic capability of genomic information has been clinically validated.^{1,2}

It seems reasonable to predict, for example, that in the next decade or sooner, a majority of health plans will make it easy for

their members to have their entire genomes sequenced and linked to their electronic health records and will provide software to help people interrogate their own genomes, with or without the help of their physicians or a genetic counselor supplied by the health plan. This service will, of course, require a massive data bank of genome reference materials, and the FDA and the National Institute of Standards and Technology are collaborating on the development of reference materials.² Before genomic tests have been validated, however, genomic information can be misleading — or just plain wrong — and could cause more harm than good in health care settings. In most cases, family history is likely to be at least as informative about an individual's health risks as SNP-based testing like that used by 23andMe. In this regard, the FDA's warning letter to 23andMe for its non-validated PGS, which resulted in 23andMe's ceasing to sell its product, is not currently depriving people of useful information; the agency is merely requiring that companies that want to sell their health-related medical devices to the public demonstrate to the FDA that they are safe and effective — in this case, that the tests do what the company claims they do. That is traditional consumer protection and what the public expects from the FDA.

Privacy is a closely related issue. How can the extremely private and personal information locked in our DNA be protected so that others cannot use it for their own purposes without our consent or make it available to people or organizations who could use it against us (e.g., by

denying us life or disability insurance)? 23andMe has, for example, suggested that its longer-range goal is to collect a massive biobank of genetic information that can be used and sold for medical research and could also lead to patentable discoveries. Such uses seem reasonable so long as the consent of the DNA donors is properly obtained and their privacy is protected. Both of these requirements are, however, much more difficult to uphold than 23andMe seems to realize.³

Informed consent to genomic testing is the subject of a wide-ranging debate, touched off by testing policies published by the American College of Medical Genetics and Genomics (ACMG). Their recommended guideline requires that when a physician orders a clinical sequencing test, the laboratory also test for pathogenic (or probably pathogenic) mutations in 56 genes, related to 24 serious disorders. According to an ACMG clarifying statement, “patients cannot opt out of the laboratory’s reporting of incidental [secondary] findings to the ordering clinician” (www.acmg.net). Such a requirement does not amount to informed consent but represents a waiver of the right to decide what tests will be performed. People have both a right to know what will be done to diagnose their condition and a right not to know about their genetic predispositions if they don’t want to know.^{4,5} 23andMe had adopted a more rights-respecting mode here — giving customers a second chance not to find out about the results of specific tests (such as tests for breast-cancer mutations, Parkinson’s disease, and Alzheimer’s disease) after the test is done (see screen shot).⁴

Whole-genome screening, whether ordered by physicians or consumers, will require more sophisticated informed-consent protocols, and we believe that individuals should also retain the right not to have specific genes sequenced at all.⁵ James Watson set a reasonable standard for non-disclosure. He authorized the publication of his entire genome with one exception: he refuses to be informed of his APOE status or have it published because he does not want to know whether he is at higher-than-average risk for Alzheimer’s disease. That should be his right and the right of every patient or consumer.

of genomics.¹ As the cost of such sequencing continues to fall, millions of people will probably have their genomes sequenced. That will turn out to be the easy part. The difficult part will be, as it is today, the clinical interpretation of an individual’s genome and the making of useful recommendations to the patient-consumer. Put another way, **the heart of this debate is not the cost of the sequencing (or SNP testing), but rather whether the information produced can be used in ways that improve our health.** We think that the goal of the FDA and 23andMe (as well as all clinical geneticists, testing labo-

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Because of the company’s aggressive marketing and refusal to resolve outstanding data issues, the FDA was right to issue a warning to 23andMe. The resulting marketing shutdown provides the opportunity for serious dialogue that could be a basis for setting standards not just for 23andMe, but for the entire industry. 23andMe, for example, makes the consumer’s raw genetic data derived from the DNA sample accessible to the consumer, something all biobanks should do. It could also be a catalyst for creating a regulatory framework for whole-genome-sequencing platforms, which are the future

ratories, and the entire genetics industry) should be to ensure that genomic information is both accurate and clinically useful. Clinicians will be central to helping consumer-patients use genomic information to make health decisions. Any regulatory regime must recognize this reality by doing more than simply adding the tagline on most consumer ads for prescription drugs: “Ask your physician.” That is insufficient guidance unless your physician has ready access to a clinical geneticist or genetic counselor.

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From the Department of Health Law, Bioethics, and Human Rights, Boston University School of Public Health, Boston (G.J.A.); and the Department of Obstetrics and Gynecology, Feinberg School of Medicine, Northwestern University, Chicago (S.E.).

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Incidentalomas in Genomics and Radiology

Benjamin D. Solomon, M.D.

The availability of new technologies has made high-throughput genomic sequencing increasingly prevalent in both research and clinical fields. Such sequencing includes targeted methods, such as exome sequencing, which focuses on the functionally important regions of known genes, as well as whole-genome sequencing. As the use of these methods grows, it is important to accurately describe both their potential and their inherent challenges.

One controversial area involves the handling of the range of medical information found through genomic sequencing.^{1,2} This may include genetic or genomic data that are unrelated to the primary reason for conducting sequencing but may be medically important. For example, when genomic sequencing is performed to seek an explanation for an infant's multiple congenital anomalies, thorough DNA analysis may reveal a genetic variant that is not known to be related to the anomalies but that indicates high risk for certain cancers.

Being able to describe the

types of medical information that may be found through genomic sequencing (see table) is important for activities such as designing and implementing research studies, obtaining consent from participants or families, and describing testing methods and results to patients and families. Since these complex issues can be difficult to explain, the analogy of an unexpected radiologic anomaly, such as a lesion incidentally or secondarily seen on a chest x-ray, is commonly used.

In both the genomic and the radiologic situations, in order to explore the available options and determine the most appropriate medical course, one must find out more about the additional finding. For radiologic findings, such a pursuit could include more precise imaging techniques and a biopsy for pathological analysis. Some lesions will turn out not to be of concern, whereas others may be shown to represent, for example, a cancer. A potential benefit is that sometimes treatment may be initiated earlier than it would have been if the condition had been noticed only when it became symptomatic.

Risks include false positive findings that might result in unnecessary testing and psychological harms.

For genomic findings, the next steps after variant identification involve examining the evidence regarding the pathogenicity of the variant and any involvement in disease. Some variants are easy to classify in terms of disease involvement. For example, there is strong evidence that certain variants cause genetic disorders. One approach involves attempting to limit the incidental or secondary informatic analysis to those variants, but that might result in ignoring important health information.¹ Other previously unreported variants in genes that are known to be involved in human disease may, because of their variant type, be predicted to cause disease; examples might include a whole-gene deletion or a truncating mutation. Many variants are even more difficult to interpret, including variants in genes involved in well-characterized mendelian disorders. In such instances, evaluating variant pathogenicity may include querying databases of both reported mutations and