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VIEWPOINT

23andMe, the Food and Drug Administration, and the Future of Genetic Testing

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On November 22, 2013, the US Food and Drug Administration (FDA) effectively halted health-related direct-to-consumer genetic testing in the United States by sending a warning letter to 23andMe, the leading company in the field, directing it to stop providing such testing.[1] The FDA acted as the era of widespread, clinical use of DNA sequencing rapidly approaches. The agency's action will contribute to changes in which genetic tests are offered to patients and how testing is provided.

Since 2007, Mountain View, California–based 23andMe has offered—directly to consumers, via its website—a "Saliva Collection Kit and Personal Genome Service." The service identifies single nucleotide polymorphisms, or SNPs, variations of individual base pairs within the genome, using a microarray, often referred to as a *SNP chip*. Based on its analysis of SNPs, 23andMe provided consumers with health-related information concerning 254 diseases and conditions as well as information on genealogy (such as percentage of Neanderthal ancestry) and nondisease traits (dry- vs wet-type ear wax, for example). However, SNPs rarely affect health directly. Instead, SNP-based health information typically is based on statistical correlations between SNPs and phenotypic traits that are found in whole-genome association studies.

The FDA regulates genetic testing products as devices when they are "intended for use in the diagnosis…or prevention of disease."[2] Although the FDA has long considered health-related genetic tests to be within its jurisdiction, it has not regulated many of them. The agency has chosen not to regulate genetic tests developed by a laboratory for its own use that are not a premanufactured "kit," perhaps because those tests are regulated in part by the Clinical Laboratories Improvements Amendments Act and are the subject of guidelines from the College of American Pathologists.

The FDA's primary concern with medical devices is whether they are safe and effective for their intended use. For genetic tests, *effectiveness* encompasses 2 concepts: analytic validity, how well the test measures what it purports to measure; and clinical validity, the accuracy of the results with regard to the presence or absence of a disease or condition. Using 23andMe's kit as an example, analytic validity is correctly identifying SNPs, and clinical validity is accurately reporting any health consequences. Notably, 23andMe provided this information directly to consumers. Consumers could seek a physician's or a genetic counselor's advice about the meaning of the results but were not obliged to.

The FDA ordered 23andMe to stop marketing its personal genome service because it is an unapproved and uncleared device. The company's website had called its personal genome service "the first step in prevention"[1] of diseases such as diabetes and cancer, which clearly sounds like something "intended for use in the diagnosis . . . or prevention of disease,"[2] the statutory definition of a device.

The warning letter further explained that 23andMe must obtain the agency's authorization for each of the test's 254 health-related uses, in essence, requiring that 23andMe show that each use is both analytically and clinically valid. Although 23andMe's service is generally thought to be analytically accurate, it may nonetheless be impossible for the company to meet both standards because the medical meaning of SNPs is often uncertain. In 2009 and 2010, 3 groups assessed the clinical validity of SNP testing results by sending identical samples to different companies that marketed genetic tests directly to consumers.[3-5] The risk assessments differed markedly. In one study,[3] about a third of the time, one company identified the SNPs of a customer as indicating a high risk for disease; another company identified the same polymorphisms as low risk.[3]

The FDA also expressed concern about delivering health-related results directly to consumers. Even if the clinical interpretation were correct, consumers might draw the wrong medical conclusion from the results without professional guidance. They might overreact to bad news through inappropriate interventions, such as changing the dose of a medication, or overreact to good news by, for example, avoiding still-useful medical interventions, such as mammograms, after receiving genetic information about their breast cancer risk.

After a vague initial response,[6] 23andMe announced that it would stop providing health information to new customers.[7] The company, however, continues to market its personal genome service, but only provides "ancestry-related genetic information and . . . raw data without 23andMe's interpretation."[7] Although 23andMe could eventually challenge the FDA in court, such a challenge would probably not succeed. It is more likely that 23andMe would work to provide the FDA with evidence that its tests are safe and accurate, although it is not clear what evidence the agency would require.

If 23andMe is unable to satisfy the FDA that its test is safe and effective, the warning letter may mark the end of direct-to-consumer genetic testing in the United States. In 2012, 23andMe's main competitors, Navigenics and deCODEme, were sold to other firms, which quickly stopped offering direct-to-consumer tests. Some smaller firms continue to offer such tests, although in the aftermath of the FDA's warning to 23andMe, they, too, may stop.

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Genetic testing delivered through medical professionals, however, will continue and grow. The FDA warned 23andMe because its tests were sold as kits. Had a doctor ordered genetic tests from a clinical laboratory that used tests it had developed, the agency, under its current policy, would not have intervened, even if the results had questionable clinical validity.

Even this kind of genetic testing will change, thanks to both technology and regulation. Sequencing of the whole genome and exome, the portion of the genome that codes information for protein synthesis, is rapidly overtaking SNP chip or single-gene tests. The human genome can now be sequenced in about 24 hours. Over the last decade, the cost of whole-genome sequencing with high-throughput (next-generation) genomic sequencers has fallen from roughly $500 million to less than $5000. The move to this next-generation sequencing is already happening, both in industry and at FDA. On November 19, 2013, 3 days before sending the warning letter to 23andMe, the FDA authorized Illumina, a biotechnology company based in San Diego, California, to market 4 next-generation sequencing products: a sequencing platform, 2 tests for cystic fibrosis that use the platform, and a "universal kit" that allows laboratories to use the platform and develop their own tests for any genetic variation.[8]

The FDA's authorization of a high-throughput sequencing platform, cystic fibrosis tests, and universal kit was presumably based on a favorable assessment of their analytic validity. But the authorization for a universal kit was not accompanied by a requirement that the clinical validity of the testing be demonstrated. Thus, patients could be told that they have particular genetic variations without any regulation of the explanations from laboratories of what those variations mean.

The FDA has said, without disclosing details, that it is interested in a risk-based approach to regulating genetic tests that are developed by laboratories. Stronger regulation would be applied to tests that are deemed riskier. The continued delay in announcing a proposed policy might reflect the inherent difficulty of determining clinical validity for genetic tests. For example, although the clinical validity of some gene variations is well known—2 copies of the ΔF508-*CFTR1* allele lead to cystic fibrosis, and the 185delAG deletion in *BRCA1* exposes women to a significantly higher risk of breast cancer—many stretches of DNA have either only weak evidence for their health effects or are simply variants of unknown significance.

The FDA's warning letter to 23andMe marks the end of the agency's willingness to allow unverified health claims for direct-to-consumer genetic tests. Whether it marks the end of direct-to-consumer genetic testing depends on the FDA's standards for their clinical validity. The agency's nearly simultaneous authorization of the first next-generation genetic sequencing products marks the beginning of large-scale whole-genome and exome sequencing for clinical use. But the application of these technologies also depends on the standards for clinical validity. Requiring proof of clinical validity for each variant would halt most, if not all, genetic testing. But if the FDA does not require any evidence of clinical validity, it would invite chaos—and quacks. We may have reached the end of one regulatory and technological era for genetic testing, but another is just beginning.

ARTICLE INFORMATION

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