VIEWPOINT

# Innovation, Risk, and Patient Empowerment
## The FDA-Mandated Withdrawal of 23andMe's Personal Genome Service

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**On November 22, 2013,** the US Food and Drug Administration (FDA) took the surprising step of ordering 23andMe, a genomics company, to cease marketing its flagship Personal Genome Service (PGS). The PGS is a DNA sequencing product marketed directly to consumers that claims to "help individuals and their doctors identify health areas that they need to keep an eye on." By determining the presence of certain single-nucleotide polymorphisms, the PGS estimates risk for more than 250 diseases and health conditions by extrapolating from research studies. After initially continuing to sell its product, 23andMe heeded the FDA's warning letter and stopped offering health-related genetic tests on December 6, 2013.

The PGS is a patient-centric tool that provides consumers a wide array of genetic information. For instance, it provides information on many of the 58 gene mutations associated with 24 genetic disorders that the American College of Medical Genetics and Genomics recommends reporting to patients if incidentally discovered during genetic testing,[1] mutations for which there is strong evidence that information can benefit patients. However, the PGS also estimates risk of more than 200 other health conditions, such as diabetes mellitus, celiac disease, and restless legs syndrome. Even though this information may empower patients, its role in clinical practice is unclear.

For example, FDA-approved labels of warfarin anticoagulants recommend pharmacogenetic dosing if patients' genotypes are available; however, recent clinical trials have cast doubt on the benefits of systematic genotyping. Other components of the PGS, such as those estimating risk of restless legs syndrome, are based on preliminary evidence. The PGS bundles all of these genetic tests into a single product, which is marketed directly to consumers using the Internet, radio, and television,[2] and does not allow ordering of selected tests. The product has been purchased by more than 500 000 individuals, but it was never approved by the FDA.[2]

Medical devices, which include diagnostics like the PGS, are regulated by the FDA and generally require review through 1 of 2 regulatory pathways. Class I (eg, tongue depressors) and class II devices (eg, computed tomography systems) are estimated to place patients at low risk of harm and generally do not require clinical testing; they require only notification and registration with the FDA via the 510(k) process, which involves determination of whether the new device is "substantially equivalent" to an existing device already available on the market.[3] Class III devices (eg, implanted prosthetic valves) are estimated to have a higher risk of harm and require approval by the FDA prior to market availability to provide "reasonable assurance" of safety and effectiveness based on clinical testing.

Innovative products for which there is no existing substantially equivalent product challenge this regulatory framework. Historically, such devices were classified as class III and required clinical testing. However, the 1997 FDA Modernization Act allowed the agency to classify lower risk devices without substantially equivalent predicates as class I or II, diminishing premarket clinical testing requirements. This approach was used in the FDA's recent approval of MiSeqDx, a next-generation sequencing platform that allows customized, and not just disease-specific, genetic testing as a class II device.

According to the FDA's warning letter,[2] 23andMe submitted several 510(k) clearance applications during 2012, indicating that the company was seeking approval as a class II device almost 5 years after the PGS was made available to consumers. The FDA rejected these 510(k) applications after the company failed to provide requested information.[2] Although the exact content of these requests was redacted, the warning letter noted that the PGS was not substantially equivalent to an existing device,[2] a designation that opened the door to the risk-based classification established by the FDA Modernization Act.

Because 23andMe was able to market the PGS without regulatory approval, there is a paucity of data characterizing the accuracy of both its sequencing process and its estimates of disease risk. Obtaining accurate DNA sequences from the PGS requires multiple steps, including proper sample collection, transport, and storage, as well as precise sequencing. Error can be introduced at any step, with the more than 250 conditions magnifying the possibility of inaccurate result. Data demonstrating sequencing accuracy are emerging as a prerequisite for FDA approval of genetic tests. In classifying the MiSeqDx as a class II device, the FDA reviewed validity and quality data demonstrating that the product could accurately sequence a variety of well-characterized genes.[4]

Moreover, even if the correct DNA sequence is determined, the accuracy of the estimates of disease risk made by the PGS must be evaluated because they are based on extrapolations of research associating specific genetic sequences with the risk of clinical disease. A Government Accountability Office investigation of direct-to-consumer genetic tests in 2008 noted that companies testing the same genetic samples produced divergent, and sometimes direc-

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tionally different, estimates of disease risk, highlighting inconsistencies among the products.[5] The algorithms and data used to produce these risk estimates must be frequently updated and publicly available for input. Even if these steps are taken, most estimates of disease risk determined through genetic testing are simply best estimates based on extrapolation of observational data with uncertain clinical implications.

The potential effect of inaccurate results obtained using the PGS was magnified by its direct availability to consumers. For example, the FDA suggested that patients taking warfarin might adjust their dose independently (leading to higher rates of thrombotic or bleeding events) on the basis of information about warfarin metabolism provided by the PGS.[2] In the absence of data, it is impossible to determine if the agency's concerns were well-founded and if the PGS is appropriate for independent patient use. In addition, the potential clinical benefit of information obtained from the PGS remains unclear. Unlike a chest film that confirms a pneumonia diagnosis, genetic testing is intended to predict the potential risk for disease in the future. The recommendations[1] of the American College of Medical Genetics and Genomics highlight that the disease risk is rarely treated. Although some uncertainty may be acceptable, inaccurate diagnostic tests do carry risk and have been associated with long-term psychosocial sequelae and higher health care costs.[6,7]

The PGS is an example of a disruptive product that challenged the FDA's existing regulatory framework. With few data on which to base a decision, the FDA took an unusual action by mandating withdrawal of the PGS largely on the basis of its theoretical risk of harm that could result from inaccurate estimates and interpretations of disease risk, although the accuracy of the sequencing process used by the PGS also was not demonstrated. The apparent emphasis on theoretical harm is significant because historically the FDA has been a reactive regulator, waiting for evidence of actual harm to accumulate before acting.

Additional data characterizing the accuracy of the PGS, including that of its sequencing process and estimates of risk, could facilitate its reintroduction. When it becomes clear that the sequencing process used by the PGS is accurate, the use of this product could be allowed under the supervision of a physician. Direct-to-consumer and office-based genomic testing will only become more common in clinical care with physicians playing a critical role by contextualizing test results. Physicians can help to inform patients about decisions regarding approaches to address any increased risk for clinical disease, which is an especially important responsibility in light of the FDA's concerns about the potential adverse effects of unsupervised use of the PGS. In addition, this approach would allow continued empowerment of patients to seek out additional health information. However, resumption of direct-to-consumer sales should only be permitted once meaningful data have been generated confirming that the estimates of disease risk made by the PGS are accurate and that the product can be used safely without medical supervision.

## ARTICLE INFORMATION

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