FDA 23andMe Personal Genome Service (PGS) Test – Evaluation of Automatic Class III Designation – De Novo Request (Memorandum)

Grants FDA approval to the 23andMe Personal Genome Service (PGS) test as a Class II medical device for ten diseases and conditions and outlines special controls to mitigate risks involved.

Updated last **November 7, 2017**
for the 04/06/2017 memorandum.

WHAT IT DOES

On April 6, 2017 the Food and Drug Administration (FDA) published a memorandum classifying the Personal Genome Service (PGS) Test by 23andMe as a Class II device and approved that device for assessing ten diseases and conditions. This approval means the public may use this direct-to-consumer genetic test to learn about their genetic risks for certain conditions.

The FDA approved the PGS test for the following diseases and conditions, while noting in each case that the test does not describe a person's overall risk of developing a certain condition but rather indicates the person possesses certain DNA variants associated with the conditions:

1. Hereditary Thrombophilia
   - Describes increased risk of developing blood clots
   - Most relevant for those of European descent
2. Alpha-1 Antitrypsin Deficiency
   - Describes increased risk of lung or liver disease
   - Most relevant for those of European descent
3. Late Onset Alzheimer's Disease
   - Describes increased risk of developing late onset Alzheimer's disease
   - Most relevant for those of European descent
4. Parkinson's Disease
   - Describes increased risk of Parkinson's disease
   - Most relevant for those of European descent, Ashkenazi Jewish descent, and North African Berber descent
5. Gaucher Disease Type 1
   - Describes increased risk of Gaucher disease
   - Most relevant for those of Ashkenazi Jewish descent
6. Factor XI Deficiency
   - Describes increased risk of excessive bleeding following trauma or surgery
   - Most relevant for those of Ashkenazi Jewish descent
7. Celiac Disease
   - Describes increased risk of developing Celiac disease
   - Most relevant for those of European descent
8. Glucose-6-Phosphate Dehydrogenase (G6PD) Deficiency
   - Describes if a person has a variant associated with G6PD deficiency and an increased risk for episodes of anemia
   - Most relevant for those of African descent
9. Early Onset Primary Dystonia
   - Describes increased risk of developing early onset primary dystonia
   - Most relevant for those of Ashkenazi Jewish descent
10. Hereditary Hemochromatosis
    - Describes if a person has variants associated with hereditary hemochromatosis and a higher risk for iron overload

- Most relevant for those of European descent

The FDA's risk assessment, conducted as part of the *de novo* medical device classification process, identified three risks to patient health the PGS test presents:

1. Incorrect understanding of the device and test system;
2. Incorrect test results (false positives, false negatives); and
3. Incorrect interpretation of test results.

To mitigate the above risks, the FDA memorandum established special controls on the PGS test.

1. Labeling must include the following information for users:
   - A disclaimer that the test does not report on the user's entire genome, but instead on specific variants. The test [does not/may not, as appropriate] detect all genetic variants related to a given disease. If the test results show that the user does not have an increased risk of having a particular disease, that does not mean that they have no risk for that disease;
   - A disclaimer that the same user may receive different results from different companies' tests due to the fact that each company uses different variants to determine disease risk;
   - A disclaimer that environmental and lifestyle factors impact disease risk as well as genetic variants;
   - Advice that if the user is nervous or anxious about testing, they should consult with their physician or healthcare professional. The 23andMe PGS test and generic equivalents are not a substitute for visits to a doctor of healthcare professional;
   - Information on how to obtain access to a genetic counselor or professional equivalent;
   - A disclaimer that this test is not intended to diagnose disease, tell the user anything about their current state of health, or be used to make medical decisions, including what medications the user should or should not take; and
   - A disclaimer that the laboratory may not be able to process the user's sample.
2. Labeling must include the following disclaimers for healthcare professionals who receive a patient's test results:
   - This test is not intended to diagnose disease, tell the professional anything about the current state of health of their patient, or be used to make medical decisions;
   - This test is intended to provide users with their genetic information to inform lifestyle decisions and conversations with doctors and healthcare professionals; and
   - Any diagnostic or treatment decisions should be based on testing and or other information that the professional determines to be appropriate for their patient.
3. The genetic test must be used with a sample collection device that is FDA-cleared, -approved, or -classified as 510(k) exempt, with an indication for in vitro diagnostic use in over-the-counter DNA testing.
4. Labeling must include hyperlinks to the manufacturer's public website, where information including but not limited to the following is available:
   - Basic explanations of how the test works and how to interpret results;
   - Definitions of all terms;
   - Genetic variants used in each disease risk evaluation;
   - Scientific justifications that correlate these genes to disease risk;
   - Every step of diagnostic DNA isolation, analysis, and evaluation;
   - Risk mitigation strategies;
   - Information regarding test failure;
   - Performance characteristics of the test; and
   - The clinical performance summary.
5. The PGS test is *not* approved for the following:
   - Prenatal testing;
   - Predisposition to cancer where the result of the test may lead to prophylactic screening, procedures, and treatments that may incur mortality or morbidity (for example: *BRCA1* and *BRCA2* genes associated with predicting risk for breast cancer, since patients might then pursue preemptive treatments like chemotherapy or mastectomies);
   - Assessing the presence of genetic variants that impact metabolism, exposure response, risk of adverse events, dosing, or mechanisms of prescription for over-the-counter medications;

- Assessing the presence of deterministic autosomal dominant variants (for example: Huntington's disease is determined by the inheritance of one gene).

Alongside its approval of the 23andMe PGS test, the FDA created a new category of medical products, known as Genetic Health Risk Assessment Systems, and classified the PGS test as such a product. As defined by the FDA in the memorandum, a Genetic Health Risk Assessment System is a qualitative molecular diagnostic system used for detecting variants in genomic DNA isolated from human specimens that will provide information to users about their genetic risk of developing a disease to inform lifestyle choice and/or conversations with a healthcare professional. This assessment system is for over-the-counter use and does not determine the person's overall risk of developing a disease. This existence of this new category will allow future genetic tests issued by 23andMe or other companies to receive approval by demonstrating 510(k) substantial equivalence, rather than using the *de novo* process.

RELEVANT SCIENCE

Predictive and pre-symptomatic genetic testing, the type of genetic testing employed in the 23andMe PGS test, is the analysis of an individual's DNA sample to identify specific genetic variants (i.e., uncommon alterations in a DNA sequence) associated with certain diseases or conditions. If an individual's DNA contains a specific variant that has been connected to a disease or condition, that person has a certain risk of having that disease or condition. But possessing any given variant does not necessarily mean the individual will eventually develop the disease or condition.

Multiple limitations exist regarding genetic testing. Many different variants have been associated with disease, however the vast majority of these associations have not been definitely proven. Additionally, direct-to-consumer tests (i.e., genetic tests that can be purchased directly by consumers without prior consultation with their physician) have varying degrees of accuracy and validity. Furthermore, since the vast majority of genetic variant studies are conducted on individuals of European ancestry, genetic testing might not be as accurate a predictor of disease risk in individuals without such ancestry.

RELEVANT EXPERTS

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BACKGROUND

The FDA separates medical devices into three classifications:

1. Class I devices carry low risk and are subject to the least regulatory controls (e.g., dental floss).
2. Class II devices are higher risk than Class I and require greater regulatory controls to provide reasonable assurance of the device's safety and effectiveness (e.g., condoms).
3. Class III devices are the highest risk and are therefore subject to the highest level of regulatory control. These devices must be approved by the FDA through testing before they are marketed (e.g., replacement heart valves).

Many medical devices produced by companies have similarities to existing devices or improve upon existing medical devices. The 510(k) process allows companies to prove that their new device has substantial equivalence to a legally marketed, previously approved device (a "predicate".)

A device is substantially equivalent if, in comparison to a predicate, it either:

1. Has the same intended use as the predicate and has the same technological characteristics as the predicate; or
2. Has the same intended use as the predicate and has different technological characteristics as the predicate, but the

supplementary information submitted to FDA:

1. Does not raise new questions of safety and effectiveness; and
2. Demonstrates that the device is at least as safe and effective as the legally marketed device.

As the FDA points out, a claim of substantial equivalence does not mean the new and predicate devices must be identical. Substantial equivalence is established with respect to intended use, design, energy used or delivered, materials, chemical composition, manufacturing process, performance, safety, effectiveness, labeling, biocompatibility, standards, and other characteristics, as applicable.

De novo classification is a process for medical device approval when there is no substantially equivalent predicate. Medical device manufacturers have two options for *de novo* classification:

1. If the manufacturer submits a 510(k) clearance and receives a "not substantially equivalent" (NSE) determination from FDA, they may request, within 30 days of receiving the determination, that the FDA make a risk-based classification of the device; or,
2. If there is no legally marketed device upon which a determination of substantial equivalence can be based, the manufacturer may request the FDA to make a risk based classification under without first submitting the 510(k) clearance.

ENDORSEMENTS & OPPOSITION

- Sharon Terry, CEO of Genetic Alliance, interview response, April 7, 2017: "Women learn they are pregnant using a test directly marketed to them and buy it off the shelf in a drugstore. In 10 years we will marvel that this [approval of a genetic test] is an 'advance' at all. Imagine pregnancy tests being only available through a doctor!"
- Robert Green, medical geneticist at Harvard University, interview response, April 6, 2017: "We're moving as a society toward empowering people with health related information and this is, I think, a welcome step, along that journey."
- Brendan Frey, CEO of Deep Genomics, interview response, April 10, 2017: "This a conservative set [of diseases], there's a very, very low risk in terms of getting it wrong. The newly approved tests are for well-understood mutations that are associated with substantial increases in disease risk."
- Mary Freivogel, president of the National Society of Genetic Counselors, interview response, April 7, 2017: "Direct-to-consumer testing takes away a pre-test conversation.... [Genetics are] one piece of the story."
- Gail P. Jarvik, medical geneticist at the University of Washington, interview response, April 6, 2017: "If people know what they are purchasing and understand the results, then I support such tests. It is in the execution that my concerns lie and I will be following that. We have seen patients who did not understand tests they purchased from this company in the past. Hopefully, this information will be delivered in a way that has value to the person purchasing the service and does not cause unneeded medical visits. Many of these tests indicate risk of getting disease, not the certainty of getting it."
- Hank Greely, director of Center for Law and the Biosciences at Stanford University, interview response, April 6, 2017: "It could be worse. It might not be a bad thing. I'm not enthusiastic. I'm not convinced this will improve Americans' health or make consumers better off. But I'm not convinced that it won't."

STATUS

On November 7, 2017, the FDA formally published the order in the *Federal Register* (82 FR 51560) classifying any substantially equivalent genetic health risk assessment system into class II, and establishing the relevant category within the Code of Federal Regulations.

RELATED POLICIES

The Food Drug and Cosmetic Act (FDCA; 21 U.S.C. 301 *et seq.*) describes the administrative structure, guidelines, and procedures that the FDA follows in all drug and device approvals.

The Food and Drug Administration Safety and Innovation Act (FDASIA; Public Law 112-144), enacted July 2012, made amendments to the FDCA, including the applicability of *de novo* classification requests for low- or medium-risk devices without first receiving the 510(k) clearance.

POLICY HISTORY

23andMe first launched its direct to consumer tests for individual genetic testing in 2007. The FDA intervened in November of 2013, claiming that the company did not have the authority to diagnose diseases nor to offer suggestions and guidance on how patients could reduce certain health risks. The FDA stated the direct to consumer tests marketed by 23andMe are considered a medical device by the FDA and no medical device can be marketed without FDA approval. In 2015, the FDA approved 23andMe for carrier screening in adults of reproductive age and for a clinically relevant gene mutation associated with cystic fibrosis.

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