How Should Patients and Providers Interpret the US Food and Drug Administration's Regulatory Language for Direct-to-Consumer Genetic Tests?

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Introduction

A healthy 30-year-old woman with no family history of breast or ovarian cancer learns that she carries a pathogenic *BRCA1* mutation through a direct-to-consumer (DTC) *BRCA1/BRCA2* genetic test. She shares this result with her primary care physician and expresses a strong interest in having a prophylactic mastectomy as soon as possible. While looking through her test report, the physician comes across a disclaimer warning that “Results should be confirmed in a clinical setting before taking any medical action.”¹ When he suggests that she undergo confirmatory testing, she shows him the press release from the US Food and Drug Administration (FDA) affirming that the test is accurate and provides reproducible results.² A company-authored blog entry also insists that the test's results are highly accurate and meet FDA requirements for analytical, clinical, and scientific validity.³ She does not want to pay for repeat testing out of pocket, and her insurance will not cover confirmation because she does not meet clinical criteria for *BRCA* testing. Both the patient and her physician are confused as to why confirmatory testing is necessary if the results are accurate. The physician is left wondering whether he should insist on confirmatory testing or just refer the patient to a breast surgeon.

This article examines the FDA's regulatory language as it relates both to the diagnostic significance and medical actionability of DTC test results and, in addition, to the need for confirmatory testing. Using the *BRCA1/BRCA2* test from 23andMe (Mountain View, CA) as an example case, we consider how this language might confuse not only consumers, but also medical providers who are asked to interpret results and make clinical recommendations.

23andMe's *BRCA1/BRCA2* Test: A Case Study

Last year, the FDA authorized 23andMe to market its *BRCA1/BRCA2* test, making it the first FDA-authorized DTC genetic test for cancer risk.² Currently, 23andMe is only authorized to test for three specific mutations—two in the *BRCA1* gene (*BRCA1* c.68_69delAG and *BRCA1* c.5266dupC) and one in the *BRCA2* gene

(*BRCA2* c.5946delT)—that are found almost exclusively in the Ashkenazi Jewish population.

The FDA's decision to authorize 23andMe's *BRCA* test is part of a larger regulatory trend toward greater consumer access to health-related genetic information. This trend began in February 2015 when the FDA authorized 23andMe to market a genetic test to identify carriers of Bloom syndrome, an autosomal recessive disorder that causes short stature, photosensitive skin, and an increased risk of cancer.⁴ Two years later, in April 2017, the FDA authorized 23andMe to market a genetic test that provides information about whether an individual carries certain genetic markers associated with 10 health conditions, including a variant in the *APOE* gene associated with late-onset Alzheimer disease.⁵ At the time, these were the first FDA-authorized DTC genetic tests to provide information about an individual's genetic risk for specific health conditions. In March 2018, the FDA authorized 23andMe to expand its Genetic Health Risk reports to include *BRCA1/BRCA2* testing.² We have chosen to focus on 23andMe's *BRCA* test because it reports on *BRCA1/BRCA2* variants that have significant implications for cancer risk and medical management. Moreover, unlike most other health-related DTC genetic tests, including 23andMe's *APOE* testing, there are well-established clinical guidelines for *BRCA* testing and the management of individuals with documented mutations.⁶

Before granting authorization, the FDA reviewed data for 23andMe's *BRCA* test through the de novo pre-market review pathway, which is a regulatory route for novel, low- to moderate-risk devices that are not equivalent to a device that is already being legally marketed. On the basis of its review of the test, the FDA determined that the company had provided sufficient data to demonstrate that the test is accurate, can deliver reproducible results, and is generally easily understood by consumers.²

Commentaries on the FDA's decision to authorize 23andMe's *BRCA* test have, so far, focused on the test's limitations, with a major one being that an individual

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who receives a negative result could still carry a different *BRCA1/BRCA2* mutation or a mutation in another cancer susceptibility gene.^{7,8} Although the FDA has repeatedly emphasized that a negative result does not rule out increased cancer risk, we worry that some of the language surrounding certain regulatory requirements may undermine consumers' and providers' ability to understand the test's purpose and the clinical implications of results.

What is the Diagnostic Significance of the Test?

The FDA requires that 23andMe specify that its test “does not diagnose cancer or any other health conditions and should not be used to make medical decisions.”⁹ Characterizing the test as nondiagnostic appears at odds with the description of the test as a “qualitative in vitro molecular diagnostic system.”⁹ Although it is true that a genetic test cannot diagnose cancer or determine a particular individual's risk of developing cancer in the future, a pathogenic *BRCA1/BRCA2* mutation is widely considered to be diagnostic for hereditary breast and ovarian cancer (HBOC) syndrome. For example, according to the Centers for Disease Control and Prevention, identification of a pathogenic mutation in the *BRCA1/BRCA2* genes by a clinically valid genetic test is sufficient for an HBOC diagnosis and sufficient for pursuing risk-management strategies, including enhanced surveillance, preventative surgeries, and chemoprevention.¹⁰ Given pervasive public messaging about the diagnostic significance of a positive *BRCA1/BRCA2* result and that the stated purpose of the test is to detect select clinically relevant variants to report on whether an individual is at an increased risk of cancer, the claim that 23andMe's *BRCA* test is not diagnostic could confuse consumers and health care providers who have been taught that a pathogenic *BRCA1/BRCA2* result equates to an HBOC diagnosis, for which follow-up care is medically indicated.

Does the Test Produce Actionable Results?

Maintaining that the results of 23andMe's *BRCA* test—which is intended to detect clinically relevant variants—should not be used to take medical action is also at odds with professional guidelines for HBOC risk management. For example, the National Comprehensive Cancer Network recommends that women who test positive for a pathogenic *BRCA1/BRCA2* mutation undergo breast screening and risk-reducing salpingo-oophorectomy.¹¹ Adding to the perplexity is the decision to identify 23andMe's *BRCA* test as a generic type of device called a Cancer Predisposition Risk Assessment System, which is “used for determining predisposition for cancer where the result of the test may lead to prophylactic screening, confirmatory procedures, or treatments that may incur morbidity or mortality to the patient.”⁹ Considered in tandem, it is challenging to reconcile the warning that the test not be used to make medical decisions with its classification as a Cancer Predisposition Risk Assessment System, where results may lead to medical interventions.

Furthermore, language stating that 23andMe's results should not be used to make medical decisions could confuse consumers who have used or encountered other DTC companies' offerings. For example, Color Genomics (Burlingame, CA) offers a DTC genetic test that analyzes 30 cancer susceptibility genes, including *BRCA1* and *BRCA2*. According to Color Genomics, its test produces medically actionable results so that “[y]ou can work with your healthcare provider to create a personalized screening and prevention plan, designed to help reduce your risk of developing cancer.”¹² By contrast, 23andMe's *BRCA* test is only intended to “describe if a woman is at increased risk of developing breast and ovarian cancer” and to “help . . . inform conversations with a healthcare professional.”⁹ But inasmuch as test results should not be used to make medical decisions, it is not clear what conversations—besides ones about repeat testing—23andMe's *BRCA* test is meant to inform.

There are, certainly, important differences between 23andMe and Color Genomics. First, whereas consumers can order 23andMe's test without a physician, Color Genomics requires a physician—either the consumer's own or one that has been provided by the company—to order tests on behalf of the consumer. Second, 23andMe and Color Genomics use different molecular techniques to analyze DNA (23andMe uses genotyping to screen for three specific *BRCA1/BRCA2* mutations; Color Genomics uses sequencing to identify the presence of any mutation in the *BRCA1/BRCA2* genes). Nevertheless, both 23andMe and Color Genomics offer clinically valid tests that are capable of accurately detecting the three *BRCA1/BRCA2* variants included in 23andMe's test. Yet a Color Genomics customer who tests positive for one of these three variants will receive an actionable result, whereas a 23andMe customer who tests positive will be instructed not to act on her results and to pursue confirmatory testing.

Is There a Need for Confirmatory Testing?

Finally, to reduce the risk of a false-positive or a false-negative result, it is recommended that consumers confirm their 23andMe *BRCA1/BRCA2* results in a clinical setting before taking any medical action. However, insofar as the FDA has affirmed that the test is accurate, consumers may struggle to understand why repeat testing is necessary, at least for the three variants included in 23andMe's test.⁵ Clinical genetic tests, after all, also carry a small risk of producing a false-positive or false-negative result. Nevertheless, patients are not typically encouraged to pursue repeat testing, unless there is reason to be concerned about the possibility of error. As more consumers approach their physicians with *BRCA1/BRCA2* results from 23andMe, providers may be unclear about why they should order repeat testing before making medical recommendations and whether failing to do so could carry liability.

Toward Greater Clarity

As illustrated by 23andMe's *BRCA* test, the regulatory language surrounding the implications of DTC genetic test results and the need for confirmatory testing has the potential to cause confusion. One way to mitigate this concern is to clarify, in consumer- and provider-facing materials, why a positive result is not sufficient for a diagnosis or for taking medical action and, additionally, why confirmatory testing is necessary for a test that meets the standards for accuracy and reproducibility. In the Decision Summary of its evaluation of 23andMe's *BRCA* test, the FDA states that "as the test is offered directly to consumers without the incorporation of a health care provider or genetic counselor this introduces the risk of incorrect sample collection and further increases the risk of result misinterpretation."¹³ Unfortunately, this important explanation is not included with the informational resources that consumers and providers are most likely to encounter, such as the company Web site and the package insert that accompanies each test. If the test is intended as a preliminary screen for certain *BRCA1/BRCA2* variants, perhaps that could be stated explicitly. This approach would help the public understand that the test is meant to function in much the same way as a home pregnancy test; like authorized DTC genetic tests, home pregnancy tests must demonstrate that they are accurate and reliable. Nevertheless, when a woman informs her provider that she is pregnant on the basis of the results of a home pregnancy test, it is standard practice to confirm the pregnancy clinically before

proceeding with prenatal care. Offering this explanation would help consumers and providers understand the reasoning behind recommendations that seem to conflict with public messages and clinical guidelines about *BRCA* testing.

Beyond clarifying test-related materials, reevaluation of the classification scheme for medical devices may be warranted. Under the current framework, medical devices are categorized into the following three regulatory classes: Class I devices present a minimal risk of harm (eg, elastic bandages); Class II devices present a moderate risk of harm (eg, powered wheelchairs); and Class III devices present a high risk of harm (eg, implantable pacemakers).¹⁴ Although the FDA classifies 23andMe's *BRCA* test as a Class II device, it is not clear that genetic tests with significant clinical implications fit within the existing regulatory structure. Accordingly, the current three-class model may need to be reevaluated to accommodate these novel types of tests.

Recognizing the public's growing interest in health-related DTC tests, there will continue to be a need to clarify the purpose and clinical significance of DTC genetic tests for disease susceptibility, especially when test results could inform medical decision making. Such attention to the appropriate use and interpretation of DTC genetic tests will help providers and patients use DTC genetic test results in a way that promotes the FDA's goal of ensuring consumer safety.

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