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Guest:
Dr. Linnea Baudhuin is Co-Director of the Personalized Genomics Laboratory, Cardiovascular Laboratory Medicine, and the Clinical Genome Sequencing Laboratory at the Mayo Clinic.

Bob Barrett: This is a podcast from *Clinical Chemistry* sponsored by the Department of Laboratory Medicine at Boston Children's Hospital. I'm Bob Barrett.

One of the largest direct consumer genetic testing facilities, 23andMe, was ordered by the US Food and Drug Administration to cease marketing its Personal Genome Service test in late 2013. This occurred after 23andMe failed to respond to questions that the FDA had about the analytical and clinical validity of this test. While some support the FDA's actions because of the test potential for harm to consumers, some advocates of the technology fault the FDA for being overly paternalistic and impeding medical advances.

In the June 2014 issue of *Clinical Chemistry*, an opinion article asks if the FDA is violating the First Amendment or protecting the rights of consumers. The author of that article, Dr. Linnea Baudhuin, is Assistant Professor of Laboratory Medicine and Pathology at the Mayo Clinic in Rochester, Minnesota, and Co-Director of the Personalized Genomics Laboratory, Cardiovascular Laboratory Medicine, and the Clinical Genome Sequencing Laboratory at the Clinic. She joins us in this podcast. Dr. Baudhuin, in general, first, what is direct-to-consumer genetic testing? And then, specifically, what is 23andMe Personal Genome Service test?

Dr. Baudhuin: Well, traditionally, genetic tests have been available only through healthcare providers. But direct-to-consumer genetic tests take a different approach in that they are genetic tests that are actually marketed directly to consumers and can be ordered directly by consumers.

If a consumer chooses to purchase a genetic test directly, what happens is that the test kit is mailed to the consumer, and then the consumer submits the sample back to the company. This may be a saliva sample or a blood sample or buccal swab. Once the testing is complete, consumers are notified of the results by mail, phone, or online. And so, really, the main point about direct-to-consumer tests is that

these tests can be purchased and results can be received without any input from a healthcare provider.

In the case of 23andMe, they have a Personal Genome Service test, also known as PGS Test. This is a $99 saliva-based direct-to-consumer genetic test. The PGS test looks for 254 health conditions and traits which include genetic disorders that are inherited in the Mendelian fashion. Take for example, hereditary breast and ovarian cancer. They include complex disorders with at least a partial genetic basis; for example, atrial fibrillation. They also include traits that may have at least a partial genetic basis; for example, propensity to heroin addiction. Their test also includes some pharmacogenetic applications such as the genetic basis for sensitivity to the drug warfarin.

23andMe requires a saliva sample from a consumer for the test. And then once the testing is completed on the sample, the company provides the test results back to the consumer through a secure online portal. The results provided by 23andMe include the genetic variants that have been detected. And prior to the FDA order to 23andMe to cease marketing its test, the results also included interpretive reports that contain risks for developing certain conditions.

Bob Barrett: Well, let's talk about that. In November 2013, the FDA did order 23andMe to cease marketing its Personal Genome Service test. Why did they do that and what are the controversies surrounding this decision by the FDA?

Dr. Baudhuin: To give you a little background to set the stage, in 2012, 23andMe actually filed for FDA 510(k) clearance for their test. Essentially, they were asking the FDA to put its stamp of approval on the test. In order to do that, the FDA requires that certain criteria are met by the company, including proof of analytical and clinical validity. The FDA said that since the filing in 2012 by 23andMe, the company had failed to respond to questions the agency had about the validity of the test.

In the letter that they sent to 23andMe on November 22, 2013, the FDA Office of In Vitro Diagnostics and Radiological Health Director, Alberto Gutierrez, stated that his office was particularly concerned about assessments for certain inherited disorder in pharmacogenetic tests because of potential risks associated with false positive or false negative assessments. He said that their office had provided ample feedback about the kinds of data it required, but the company had not yet provided adequate answers.

Gutierrez said that the FDA had already, and I quote, "Spent significant time evaluating the intended use of the PGS test to decide whether or not it could be classified as a class II

device or whether it requires pre-market approval." He also said that the FDA had proposed modifications to the PGS labeling that could mitigate any risks. But then, he went on to say in the letter, and I quote, "However, even after these many interactions with 23andMe, we still do not have any assurance that the firm has analytically or clinically validated the PGS for its intended uses, which have expanded from the uses that the firm identified in its submissions."

Prior to this letter, 23andMe had told the FDA early in 2013 that it was completing additional analytical and clinical validations, and was also planning other studies that would take months to complete. However, as of the time of the FDA letter in November, Gutierrez said his office still had not received the information it was seeking from 23andMe.

Not surprisingly, the FDA's order to 23andMe to cease marketing its test has been met with controversy. There are essentially two schools of thought on this. On the one hand, some are arguing that the government is out of line for shutting down this direct-to-consumer test and they say that the FDA is being overly paternalistic and that consumers really should have direct access to their genetic information if they want it. They also cite studies that show that consumers have only transient anxiety, if any at all, when they receive their test results. They also show studies that show that for the most part, consumers do not act on their genomic information without obtaining healthcare provider input first.

Some individuals who support this side of the controversy are even claiming that the FDA is violating the First Amendment rights of consumers on two levels. First, by violating the right of individuals to receive information; and second, by violating the right of 23andMe to advertise their test. This advertisement is a form of speech known as commercial speech.

But there is an opposing school of thought. That's that the FDA is actually protecting customers from receiving misinformation from the PGS test. This is because the 23andMe PGS test is considered a medical device. 23andMe did apply for 510(k) clearance. Therefore, this test is under the purview of the FDA. The bottom line is that 23andMe has not provided sufficient evidence that their test is analytically or clinically valid.

Bob Barrett: Well, let's go to those magic words you just said, "Analytically and clinically valid." What do you mean by that and why is it important in this case?

Dr. Baudhuin: Well, these terms are important to know. Any test that is offered in a clinical non-research based CLIA setting is subject to certain requirements to ensure that the test is performing well in some very specific categories. Laboratories need to determine these performance characteristics prior to introducing the test for patient analysis.

To define these terms, "analytic validity" is essentially how well the test predicts the presence or absence of a particular gene or genetic change. In other words, can the test accurately detect whether a specific genetic variant is present or absent? Clinical validity, the second term, is how well a genetic variant being analyzed is related to the presence, absence, or risk of a specific disease or condition.

There is another term that's important to know, and that's "clinical utility." Clinical utility is essentially whether the tests can provide information about the diagnosis, treatment, management, or prevention of a disease that will be helpful to a consumer.

So, to reiterate, the reason that these terms are important to this case is that according to the FDA, 23andMe had failed to adequately respond to the FDA regarding their questions about the validity of the intended uses of its PGS test.

Bob Barrett: Doctor, in your opinion, are there features of this test that are clinically valuable? And, well, isn't $99 for genetic test for 254 health traits and conditions almost a bargain?

Dr. Baudhuin: That's a great question. Really, some aspects of this test could be considered an exceptional value, especially for the clinically-actionable pieces of the test. For example, the inherited disorders part of the test which includes analysis for carrier status for over 50 conditions is a value when you consider that ordering each test individually would cost a great deal more than $99.

However, a huge caveat is that this panel includes only a small percentage of possible pathogenic mutations. These are usually mutations found only in specific populations and they really don't account for much of that disease's risk.

I'll give you an example. If you take a look at the hereditary breast and ovarian cancer test that looks for a pathogenic variance in the BRCA1 and BRCA2 genes, the PGS Test looks for three mutations in these genes that are common in individuals of Ashkenazi Jewish descent. However, there are actually over 2,000 reported mutations in these genes. Therefore, this test may be at least partially or significantly relevant for individuals of Ashkenazi Jewish

descent, but it's really not very applicable to non-Ashkenazi individuals.

Therefore, the concern of that is the non-Ashkenazi individuals sees their test results and see that they don't have any BRCA mutations, they may misunderstand the results and think that they have no risks for hereditary breast or ovarian cancer, when in fact, the test really has not even begun to address their risk.

That's just one example. There are several other examples of largely incomplete genetic tests for inherited disorders. These are really of limited clinical value for a large percentage of the population and they could create misperceptions among consumers who are not aware of what is missing from the test.

In addition to having incomplete inherited disorder tests, there's also a group of tests included in the PGS that are listed as, quote, "health risks." These health risks are also incomplete, and they utilize un-validated algorithms to provide a risk score. What these health risks are is over 120 disorders of known polygenic and multifactorial ideology. Some examples include atrial fibrillation, celiac disease, and restless legs syndrome. For many of these disorders, there are many known associated risk markers, but the PGS test may only look at a handful of the markers.

Additionally, an un-validated algorithm is used to provide a risk score or absolute risk or "health risk" as 23andMe calls it. This is the probability that the individual being tested will develop a condition. This absolute risk is derived using an algorithm that calculates a value for the product of all the relative risks of the genomic markers, and then multiplying this value by the average population risk for the condition. One criticism of this model is that the final average lifetime risk is dependent on which variables -- for example, age, gender, ethnicity -- are used to define population. This often varies among direct-to-consumer genetic testing companies.

Another criticism of the algorithm used is that there is a lack of weight in the risk markers, and also sometimes, genomic markers that have risk values that are too small to be statistically valid are included. Taken together, these un-validated risk analyses and incomplete testing is what has led to reports of individuals who have had their testing done at more than one direct-to-consumer companies and have received highly disparate reports of their risks.

Bob Barrett: Some published reports have said that most patients will not change healthcare actions based on the genomic data without first consulting a physician. If this is the case, why

can't consumers be trusted to obtain their genomic information directly from companies and then consult a physician downstream if they need to?

Dr. Baudhuin: Well, that's also a good question. There are really two major criticisms of this model. The first is that the majority of users of direct-to-consumer genomic tests are highly-educated and have easy access to healthcare. Their background and access to healthcare will enable them to seek out professional input on any concerning test results. There is major concern, though, that even with this easy access to healthcare, consumers likely apply subjective interpretations of genetic risk data and they may not fully understand the clinical validity or utility or limitations of their test results.

The second criticism of this is that most medical providers readily admit that they are hardly any more prepared than the general consumer to understand these reports. In fact, one study of observed that 85% of primary care physicians did not feel prepared to answer patients' questions on direct-to-consumer testing. The majority of the physicians in this study also had concerns about direct-to-consumer testing leading to incorrect interpretation of results by patients, misleading advertisements, and questionable clinical utility.

Another study found that 92% of genetic counselors perceive that patients were at risk of receiving misinformation from DTC tests, and an overwhelming 96% of them would not recommend DTC genetic testing to their patients.

The implications of all these criticisms are the potential strains that this type of test could place on the healthcare system due to the need for increased resources to educate medical providers to help them understand these unvalidated reports, and also the increased workload of healthcare providers to educate consumers about their test results.

Bob Barrett: Finally, doctor, let's look ahead. What does the future hold for 23andMe and other direct-to-consumer genetic testing companies?

Dr. Baudhuin: You know, I'm really positive about this. I think that there can and should be a place for these types of companies and tests in the marketplace. As we pointed out, these tests tend to be very affordable and they can provide some very valuable clinically-actionable information.

However, like all laboratories that provide genetic testing or any clinical testing, for that matter, direct-to-consumer

companies should focus on providing tests that will benefit the consumer. They should look at providing a more selective and clinically actionable testing menu, and that should decrease the burden placed on healthcare providers when consumers bring their test results to them.

Direct-to-consumer testing companies should also provide a mechanism to educate consumers and healthcare providers about their test, as well as help to facilitate communication between consumers and healthcare providers.

Finally, I think that direct-to-consumer testing companies should be as transparent as possible about the limitations of their test in order to avoid confusion and potentially mislead the consumer.

Bob Barrett: Dr. Linnea Baudhuin is Co-Director of the Personalized Genomics Laboratory, Cardiovascular Laboratory Medicine, and the Clinical Genome Sequencing Laboratory at the Mayo Clinic. She has been our guest in this podcast from *Clinical Chemistry*, looking at the role of the FDA and direct-to-consumer genetic testing. I'm Bob Barrett, thanks for listening.