

Bob Barrett: This is the podcast from '*Clinical Chemistry*'. I am Bob Barrett. In recent years there has been a dramatic increase in the discovery of information related to the genetic risk of disease as well as in the technical ability to accurately measure an individual's genotype. These advances underline the promise of personalized medicine, in which a patient's genotype informs the medical care they receive.

Private companies are attempting to capitalize on these advances by providing direct-to-consumer genetic testing that estimates the risk of disease for a customer given their genotype. Because these tests make claims about medical conditions, they have come under scrutiny by regulatory agencies.

In the December 2011 issue of '*Clinical Chemistry*', Dr. David Spencer, Co-Chief of the Laboratory and Genetic Medicine Department at Washington University School of Medicine, polled the opinions of several leading researchers to determine whether these breakthroughs in genetic testing are helpful or harmful to the consumer and practitioner.

Dr. Spencer is our guest in this podcast. Dr., how would you define direct-to-consumer genetic testing?

Dr. David Spencer: Well, I mean, as the name implies, direct-to-consumer testing is testing that's marketed directly to and requested by consumers, as opposed to most genetic testing which is ordered in the context of medical care by a physician, usually in response to a specific diagnosis.

Direct-to-consumer testing is ordered by an individual and is not related to any particular condition. It's kind of analogous to a prescription medication that a physician orders for a patient as opposed to say over-the-counter kind of vitamins that somebody can just pick up at the supermarket.

Bob Barrett: What do direct-to-consumer companies offer consumers that other medical labs can't provide?

Dr. David Spencer: Direct-to-consumer tests generally focus on risk of disease rather than offering a definitive diagnosis. And most genetic tests that doctors order in the hospital confirm a diagnosis or once the diagnosis has been made help the physician determine prognosis for that patient.

The direct-to-consumer genetic tests generally focus on risks of having a disease, even if that disease isn't present at that moment.

Disease risks are based on really relatively recent knowledge of how the genetic makeup of an individual at specific regions in the genome, called the patient's genotype

at those positions in the genome, might confer either the increased or decreased risk of disease. And these diseases are typically common diseases that people are concerned about, like heart disease and diabetes and that sort of thing, and the patient may or may not have those diseases at the moment, but these genotypes can inform the risk of disease in the patients.

And because the risks are conferred by these genotypes are really relatively weak compared to things like diet and exercise and family history, medical labs don't really perform the tests and physicians don't request them. So the direct-to-consumer companies are trying to capitalize on this niche and offer them directly to consumers.

Bob Barrett: Do the test require any involvement from the physician or the patient's healthcare provider?

Dr. David Spencer: No, generally not. Some of the companies do have mechanisms to kind of involve the patient's physician, but most of them the consumer can request them just by on their own, without any prescription or anything.

Bob Barrett: Just to follow-up then, a physician is going to have some information available that they really didn't request, are they going to do anything with it now that it's there?

Dr. David Spencer: Well, that's a good question! I bet most physicians are not prepared to handle this sort of information, mainly because this new knowledge I was referring to about associations between genotypes and disease are relatively new, and to be honest, the literature can be kind of confusing; some studies suggest one risk and some suggest another. And so I bet many physicians don't know exactly what to do with this information.

And my recommendation is, if a physician is confronted with these questions is to kind of make the standard of recommendations that apply to a lot of these common views is about diet and lifestyle and that sort of thing. I mean, those effects are as large, if not larger, than the ones conferred by most of the disease risks that are claimed by these companies.

Bob Barrett: Okay. Well, how are the tests performed, what sort of sample is usually required?

Dr. David Spencer: Most of these companies have you swab the cells off the inside of your cheek or deposits in saliva into a container and mail it off. After that the company extracts the DNA and labels the DNA with a fluorescent marker and applies it to a surface, and on that surface there are spots where the different genotypes are interrogated.

And depending on which of the genotypes light up with the patient's DNA, you can determine what genotype the patient has with these positions across the genome and most of these assays measure somewhere between hundreds to thousands of genotypes, even up to hundreds of thousands of genotypes, and then from that information they have a list of the risks that the genotypes may confer, either individually or kind of as a collection, the risks that are conferred for various diseases and then they issue a report based on that information.

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Bob Barrett: Are the tests very accurate and is the FDA involved in any of this?

Dr. David Spencer: The tests are not FDA approved, but medical tests don't necessarily have to be FDA approved in order to be used, so that's not really a necessity. As far as the accuracy goes, analytically meaning the same patient provides a specimen and they do the same tests and they get the same answer, in that respect they are very analytically accurate.

Most of these platforms, the concordance is more than 98%, looking across several 100,000 genotypes. So they are very accurate analytically, however as I alluded to earlier, the interpretations can be problematic.

Which study is considered when determining the risk of a genotype, what collection of genotypes you use to come up with kind of an aggregate risk, all those methods are a little more fuzzy and it depends on what method you use and what literature you are reading, what study you consider when you are assigning a risk.

And this is something that was pointed out by experts in the field that how you arrive at a final risk determination is variable and can actually lead to different risk assessments at the end of the company's report, and this has been shown in studies where they sent the same sample to multiple companies and got different answers. So that part is not as accurate, but analytically they are very accurate.

Bob Barrett: Well, from some of your answers I can tell this is generating some controversy, tell us some of the controversies around genetic testing.

Dr. David Spencer: So recently there has been a flurry of controversy because the FDA has felt like these companies may be making claims that are invalid and so they are starting to intervene, so that's kind of been the nidus for some recent controversy.

But this kind of occurs on a backdrop of how useful these tests are, as I mentioned the risks that these genotypes confer are really pretty small and for common diseases that are multi-factorial, it involves things like diet and lifestyle, these risks are really very small.

Now as we learn more, sometimes you can add up some genotypes and get to a risk that is meaningful, but in general the risk is so small that effect of these companies are asserting that they can predict your risk of heart disease or whatever is really dubious.

So there is that aspect to it, and there is also this issue of different interpretations provided by different companies, it's also sparked some controversy, I mean if you send your saliva to two different companies you get two different answers, then how useful are these tests and how valid are claims that they make?

Finally, as I said, also said earlier that are the knowledge of these associations between genotype and disease risk are really pretty new and I think there is a valid question of, do we know enough about these associations to say meaningful things?

I think many of these associations that have been reproduced by multiple groups and multiple studies are real, but this doesn't mean they are not complicated and really needs more scrutiny before we can really confidently say what the risk association is.

Bob Barrett: Well, we have been hearing more about genome sequencing lately. Will this affect genetic testing services offered to consumers?

Dr. David Spencer: Yeah, I am sure that it will and if the cost of genome sequencing continues to go down on basically a monthly basis that will make it possible for companies to not only provide genotypes just to maybe a couple of thousand or a 100,000 genotypes across the genome to consumers, but indeed their entire three billion base pair genome, and that will certainly be technically possible and probably be marketed to consumers sometime in the near future.

This will have several effects and one of them is that not only will those companies be able to provide these low, kind of, weak associations between variants and disease, but they could also identify serious mutations in the genome and in genes that could really confer disease on the patient or the patient's children. Then I think, I mean that's something that is definitely going to be possible in the near future.

Bob Barrett: Well, then let's talk about the future. Where do you see direct-to-consumer genetic testing, maybe five years from now?

Dr. David Spencer: Well, in five years we are going to learn a lot more about the genome and in particular, what mutations seem to confer a serious disease not just these associations as I mentioned, what the mutations and what genes cause clinical disease.

So as we know more about the genome, more tests can be developed and more can be said once you do this widespread genotyping or genome sequencing.

It remains to be seen how far the FDA will go in regulating these sorts of tests. It is clear though that when we know more, these companies will be able to say more to consumers, and as it gets more clinically relevant then I think it really makes sense for these tests to at least have some physician involvement to interpret the results for patients, depends how far the FDA is going to go in regulating these sorts of tests.

Bob Barrett: Dr. David Spencer is the Co-Chief of the Laboratory and Genetic Medicine Department at Washington University School of Medicine. He has been our guest in this podcast from '*Clinical Chemistry*'. I am Bob Barrett, thanks for listening!

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