Clinical Chemistry

Proposed Regulatory Framework for Direct-to-Consumer Genetic Testing: Diagnostics vs Genetic Screening

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Guest:
Dr. Ruslan Dorfman is a Molecular Geneticist and Co-founder of GeneYouIn in Toronto.

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

In December 2013 the genetics laboratory 23andMe stopped marketing direct-to-consumer disease predictive genetic testing in order to comply with a directive from the US Food and Drug Administration. The FDA's action was intended to protect the American public from questionable disease risk predictions.

However, there are some alternative views in the laboratory community. In the November 2014 issue of *Clinical Chemistry,* a letter to the editor from authors based at the Canadian Genetics Laboratory GeneYouIn appeared under the title "Proposed Regulatory Framework for Direct-to-Consumer Genetic Testing: Diagnostics vs. Genetic Screening." The lead author of that letter, Dr. Ruslan Dorfman, is a molecular geneticist, and has had a career at several major hospitals in Toronto prior to co-founding GeneYouIn. He is our guest in this podcast.

Dr. Dorfman, what is your experience with genomic sequencing in Canada, and what type of customers are you serving?

Dr. Ruslan Dorfman: So most of our customers are healthy self-referred people that are having interest in knowing the family history of disease or just curiosity, so most of them are referred either through partner clinics or through the website. We explain to all our customers that Exome Sequencing is a scanning technology and we can provide insights about various conditions, but it's not a clinical diagnostic test.

Bob Barrett: How do you administer the testing?

Dr. Ruslan Dorfman: So, our partner clinics offer the test. The customers, they have kits at hand and we collect the samples that are sent to partner labs for the sequencing. We specialize in genome analytics, so we process the data and create the reports for

our clients, and the reports are shared with clients directly and we explain them what potential disease we see may have to be shared with and we offer the same test reports to physicians with client's consent.

If we identify variance of high clinical significance we send for second revalidation to confirm the variations based on Sanger sequencing.

Bob Barrett: And what about platforms, what platforms do you use for sequencing?

Dr. Ruslan Dorfman: We used both Illumina and Ion Proton platforms, but lately we mostly use Ion Proton because if it provides shorter turn around times.

Bob Barrett: And what are the advantages and of course disadvantages of this approach?

Dr. Ruslan Dorfman: So main advantage of exome sequencing provides a very broad assessment of health risk in a single test, and although exome sequencing is not sufficiently robust to become mainstream clinical diagnostic tools, we have obtained excellent results and have been able to provide important insights about patient's inherited health risk.

One of the disadvantages of exome sequencing is the presence of batch specific artifacts that we have to be able to flag but they provide fractured approach to data analytics. The disadvantage of this approach, it has been our inability to access all family members for our clients and we have partial genetic inheritance information in both affected and inaffected family members, that makes it difficult to identify disease genomic mutations as being deleterious or not.

We feel that it is essential to investigate if these variations possibly give to clinical phenotype in the family. However, trying to collect such information has been really challenging.

Bob Barrett: Doctor, what about accuracy, how do you make sure that the results you report are accurate?

Dr. Ruslan Dorfman: We focus on genes of high penetrance and more robust phenotypes which we expect to be manifested either in patient or had been observed in the family members. So that's why we provide also with gene validation for predicting health risks in the colon, breast and skin cancers, as well as neurological diseases, diabetes, and autoimmune conditions through family history from client. So we really

get to investigate family's history and most of the time we find validation that is reported by the client.

Unfortunately for some diseases the genetic mutation is quite messy. For example, for hypertrophic meiosis the literature is quite littered with false-positive reports and in addition the clinical phenotype is not fully penetrant.

However this usually is quite universal, it also applies to establish diagnostic labs and methods, and we believe there is only a combination of curative genetic databases can solve this problem.

Bob Barrett: How have physicians and genetic counselors reacted to your genetic testing analysis?

Dr. Ruslan Dorfman: So we focus on providing continuous care for our clients and work with partner clinics and physicians, suggesting complete genetic test and use the qualified diagnosis. We are concerned about the over-reliance on results of genetic testing on disease diagnostics. We believe the genetic testing has to be viewed in the context of clinical care.

The vast majority of cases, the clinical diagnostic tests is just another assisting tool rather than primary method for disease diagnostic with exception of Mendelian diseases.

We see that genome sequencing can actually provide holistic information about the individual's current and future health. The ability to provide genetic tests and insights into conditions that have not been yet developed is most important as it offers an opportunity to prevent the disease from developing, rather than using the diagnostic test as a post-factum for confirmation.

In later scenario we feel that the opportunity to prevent the disease is already lost. We have found that partner physicians do value our test results and consider medical follow-up when necessary.

On other hand genetic counselors have difficulty to cope with large number of variants of uncertain clinical significance that is a new normal for genetic analyses.

Bob Barrett: Tell us about the regulatory challenges you anticipate with genomic sequencing?

Dr. Ruslan Dorfman: So there are several well-recognized challenges with all next generation sequencing technologies and as well as Genome and Exome Sequencing in particular.

The most difficult one is a technological challenge. We know the exome capturing protocols change all the time and

introduce great variability in coverage of specific regions. The changes in bioinformatic pipelines for genome alignment and variant calling algorithms have a significant impact on end-result, therefore we prefer to keep raw data and re-run it on different pipelines. Most importantly, we also have to accept the incompleteness of genome annotation data. There are numerous rare mutations of uncertain clinical significance which we should not ignore but rather try to characterize in detail.

We believe the regulatory bodies should viewing exome genome sequencing as a tool for scientific inquiry, and support it rather than trying to regulate it too early, because it's really too early to determine which platforms and tools really should be used for clinical diagnostics.

Just as an analogy imagine that if Henry Ford had to comply with modern safety regulations when he built the Model T, it would be very difficult in his time to comply with all these regulations, and I don't see that mass adoption of the modern automobile could have happened if the industry was so tightly regulated.

At the same time we feel that genetic testing industry becomes regulated way too quickly and we know that people have to realize that there is always inherent risk with genetic testing the same ways as using any mode of transportation.

And therefore, educated customers who understand the benefits and are ready to accept reasonable risk associated with genetic testing should be given opportunity to try it. Genetic testing provides really important results but it has to be applied responsibly, and service providers should not over-hype the benefits of genetic testing.

Genetic testing providers should provide support before and after the testing to make sure the genome sequencing results are accurate, safe, and provide effective information for improving health management.

Bob Barrett: Finally doctor, what is needed for genome sequencing to become a mainstream tool for clinical diagnostics?

Dr. Ruslan Dorfman: So, in addition to resolving the technical challenges that we discussed earlier, it's really important to provide from the traditional sample processing and data acquisition, as well as estimation of disease liability of specific variance and reporting it to the clients.

But most importantly we need to make sure that there is reimbursement of genetic testing, and both private and public insurance understand the value of the genetic testing

because it's really designed to provide preventative information for patients.

For example, it doesn't matter which type of technology has been used to determine the cause of genetic disorder as long as end results going to be deemed valid by physicians and well-recognized and accepted.

Bob Barrett: Dr. Ruslan Dorfman is a Molecular Geneticist and Co-founder of GeneYouIn in Toronto. He has been our guest in this podcast, expressing his opinions on direct-to-consumer genetic testing.

I am Bob Barrett. Thanks for listening!