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Next Generation Sequencing in Clinical Diagnostics: Experiences of Early Adopters

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Guest:
Dr. Elaine Lyon is the Senior Medical Director of Molecular Genetics and Genomics and Co-Medical Director of Pharmacogenomics at ARUP, and is Associate Professor of Pathology at the University of Utah School of Medicine.

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.

Next generation sequencing technology, also known as massively parallel sequencing, is being rapidly applied to clinical laboratory testing. Current applications include detection of inherited diseases, somatic variants in cancers, subpopulations of circulating cell-free DNA, and single viral or microbial genomes in cases of infections. Each application is unique and has its advantages and disadvantages.

The January 2015 issue of *Clinical Chemistry* published a question and answer article entitled 'Next Generation Sequencing in Clinical Diagnostics: Experiences of Early Adopters." That article presented the opinions of experts in multiple specialties such as inherited diseases, cancer, infectious diseases and prenatal genetic testing.

Today we have the lead moderator of that session, Dr. Elaine Lyon. She is the Senior Medical Director of Molecular Genetics and Genomics and Co-medical director of Pharmacogenomics at ARUP, and an Associate Professor of Pathology at the University of Utah School of Medicine.

Dr. Lyon, how has next generation sequencing been received by clinical laboratories? What are the main reasons for or against bringing the technology into the clinical lab?

Dr. Elaine Lyon: So clinical laboratories that have been doing Sanger sequencing and molecular genetic work, they have embraced next generation sequencing extremely well. Probably one of the reasons is that we could see that simply sequencing one gene at a time when many disorders have overlapping symptoms and we would need to do more than one gene, it really wasn't feasible with Sanger. And so when next-generation sequencing technology became available to

us, it was really quite easy to shift from a Sanger sequence to a next-gen sequencing platform.

However, I would say the individuals that didn't have access to informatics or people that were able to handle big data, that would be one of the reasons that it would be difficult to bring into a clinical lab. So it was first embraced by clinical laboratories that already did some Sanger sequencing and could get the resources to do the informatics portion.

The other reason to maybe hold off from bringing it in and from being an early adopter would be simply the costs of the instruments themselves.

Bob Barrett: The January 2015 feature includes next-gen sequencing application for inherited diseases, oncology, infectious disease, and prenatal testing. Why were all of these diverse applications included in the article?

Dr. Elaine Lyon: I wanted to show that one technology platform really could be useful for a lot of different applications. I also wanted, and hoped, that by getting the input from the different professionals and the different experts that the similarities for next-generation sequencing throughout these applications could become apparent, as well as the areas where they diverged dramatically and the differences that each one of these applications would need to maybe think of differently or work differently to actually have it meet what their needs were.

Bob Barrett: How would you describe the similarities and differences for next-gen sequencing with these applications?

Dr. Elaine Lyon: So for inherited diseases, we really are looking for mainly germline diseases although if we look for mosaic we may need to detect lower levels of a mutation, and most of the time we are looking for may be 50-50 mutation versus the normal or vial type sequence. In oncology they are going to need to have a much greater reads because they need to be able to detect lower levels of mutations in the samples.

So they are much more concerned about the quantitative aspect. Infectious diseases, it has not have been embraced as much yet for the clinical testing and I think it has great potential but the medical applications of really going into a microbiome-type testing hasn't been as clearly defined yet as for oncology or inherited disease.

For noninvasive prenatal testing or for the prenatal testing, it is in essence a quantitative test and so far it's the only true application to detect fetal aneuploidy in a maternal background. So, next-gen sequencing was the ideal application that we can sequence to a level and there are

several different ways you can do this, but you are really able to find a fetal genotype within a maternal background.

Bob Barrett: Doctor, the US Food and Drug Administration will be holding an open forum on regulation of next-gen sequencing testing early this year. What are your thoughts about FDA regulation of next-gen sequencing?

Dr. Elaine Lyon: Well, their open forum and workshop would be very interesting to get input from many stakeholders as the tests we've brought on lines so far have been under the CLIA regulation of laboratory developed procedures, and so we have performed everything under that.

I am encouraged by the fact that an IVD manufacturer has submitted an instrument to the FDA, and has an instrument cleared as well as a couple of assays for cystic fibrosis. And the one is for a sequencing assay, and this is actually the first inherited disease sequencing assay cleared by the FDA. And I am very much encouraged that a part of this was to make sure that it was interpreted by an appropriately qualified laboratory director, and so they are recommending that the director should be certified by the American Board of Medical Genetics or an equivalent certification to do the interpretation.

So I'm very much encouraged that the FDA is recognizing that there is a professional component that is under the practice of medicine, that it really needs to be left up to us to be able to have the freedom to interpret.

Bob Barrett: And do you feel that this view is shared by many others?

Dr. Elaine Lyon: I think it's shared by some. There are some concerns with having an instrument for clinical laboratories that it in a sense is so locked down, it becomes more difficult to develop new assays on it. But I believe that they are trying to address those concerns as well. So I would say whatever framework the FDA uses, it will need to recognize the professional component in the interpretation as well as the design of the assay, and to have an instrument that is flexible on that so we could perform multiple different types of tests on the same instrument.

Bob Barrett: Well finally doctor, let's look ahead. What do you see as the future for next-gen sequencing? Where do you see clinical labs five years from today?

Dr. Elaine Lyon: So I believe we are just going to get better at it. Right now we are learning the quality systems that need to be in place, companies are working more on the informatics, and so there will be more informatics available to us. And we will also be learning more about what human variation means,

its different efforts from a ClinGen and a ClinVar project to be able to better classify variants and to have those varied classification transparent through the efforts of a clinical geneticist and clinical laboratory directors.

So I think it will just be easier for us, the technology will get better, and hopefully with that being better it will also become less expensive so that laboratories can do more.

I would also imagine in the genetic sense--or in the inherited disease sense--that it would become more practical in essence to have one test which would be of the medical exome test and then simply report out for the specific clinical indication it had.

So, I can see next generation sequencing simplifying clinical laboratory testing. It can for oncology, I believe we would be moving into a comparison of the genome to the inherited germline versus the somatic cell mutations and again, get a better understanding of the mutations that are involved with tumor progression.

So there is a lot of research that still needs to be done, but we are capable of taking research findings and moving them fairly quickly into clinical testing so that these tests will be available for patients.

Bob Barrett: Dr. Elaine Lyon is the Senior Medical Director of Molecular Genetics and Genomics and Co-medical director of Pharmacogenomics at ARUP, and is Associate Professor of Pathology at the University of Utah School of Medicine. She has been our guest in this podcast from *Clinical Chemistry* on next-gen sequencing. The Q&A article appeared in the January 2015 issue of *Clinical Chemistry*, a special issue devoted to molecular diagnostics.

I am Bob Barrett.