Clinical Chemistry

Bioinformatics: What the Clinical Laboratorian Needs to Know and Prepare For

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Guest:
Dr. Elizabeth Chao is Director of Translational Medicine at Ambry Genetics.

Bob Barrett: This is the podcast from *Clinical Chemistry*. I am Bob Barrett.

New diagnostics technologies such as microarrays, next generation, or massively parallel sequencing, are generating an unprecedented amount of data. This requires a sophisticated knowledge of bioinformatics for proper storage, analysis, and mining of these very large data sets.

While clinical laboratories have decades of experience with informatics and in handling large numbers of results, the systems used for those tasks are largely inadequate for handling the data from -omics studies.

The September 2013 issue of *Clinical Chemistry* includes a Q&A feature where several leading investigators from academia and industry, who routinely used bioinformatics for -omics studies, were invited to discuss the importance of bioinformatics and how clinical laboratorians can best prepare themselves for handling the increasing amount and complexity of data generated by their laboratories in conducting these studies.

One of those participants was Dr. Elizabeth Chao, Director of Translational Medicine at Ambry Genetics and a former Associate Director of the Genetic Diagnostic Lab at the University of Pennsylvania. Dr. Chao joins us for this podcast.

Doctor, many laboratories are looking to launch the next generation of clinical genomics testing. What are some of the challenges that they are likely to face?

Dr. Elizabeth Chao: So moving genomics into the clinical space, I think is a challenge that a lot of laboratories are looking at and trying to figure out how to address and so the technology is now relatively mature in the research space. It's been used by a lot of research laboratories and a lot of individuals are

becoming very familiar with it, but moving that obviously into the clinical laboratory can be a huge challenge.

I think that most people probably realize that those challenges lie in two areas; number one is the bioinformatics, so being able to take that data and run the appropriate, first of all, quality checks, quality metrics, which are very different than what most labs are used to doing, but they are standard assays; and then getting past the point of quality, being able to take that data which is fairly voluminous and translate it into medically actionable and useful information for reporting out in the clinical setting.

And so I think that's sort of those two steps where the challenges lie and where this technology has yet to really mature in the clinical space with exception of the few labs that have moved there and really developing it.

Bob Barrett: How has genomics changed the process of clinical laboratory test development and validation?

Dr. Elizabeth Chao: I think genomics has sort of reinvented that process. So if you look back at the history of molecular diagnostics, there are a lot of dogma about how a test should be developed, how it should be validated, what sort of samples do you need, what constitutes the positive control and negative control, doing limit of detection assays and things like that.

Moving into the genomics space, I think a lot of that has evolved, right? So now we are dealing with massively large data sets and thinking about again going back to those quality metrics, how are you going to know whether your data looks good or doesn't look good, we have got different metrics, we have got to look out, we have got different processes, that we are looking at for confirmation, and how do you know that you are picking up what you are meant to pick up when you are not testing for just one simple alteration? But you are really out in that genomic space and you are looking for anything that could be, you know in any gene if you are running an exome test throughout the genome, if you are running whole genome sequencing. So really your measures that you are used to looking at, for example for analytic sensitivity, are very different and so that changes how you are going to develop an assay and how are going to validate it.

Bob Barrett: And so this is still an evolving process.

Dr. Elizabeth Chao: I think it is. You know even those laboratories who were early adapters or early into this space, we are all learning as we go along, the technology is obviously changing rapidly and so there are improvements not just to the sequencing

platforms, for example, but to the bioinformatic analysis, to the algorithms that we use, and so I think we are all getting better at it as we go and that's an important part of it.

Bob Barrett: How has laboratory regulatory oversight evolved or adapted over the past few years?

Dr. Elizabeth Chao: So, it has adapted, but it's been a relatively slow process and I think it's sort of ramping up as some of the oversight agencies are still getting a handle on what metrics and what measures they are going to put in place to measure how good a clinical laboratory is at doing these sorts of genomic testings. And so I think that really is an area, that's sort of still in its infancy and that some of the again early adopter laboratories are working with the regulatory agencies to say, well, these are the issues that we have accounted in test development, this is what people need to be looking out for.

So at the moment there is actually a lot of back and forth I think between the labs that are doing this and the regulatory agencies and that's so far been a pretty good relationship, as we all try to work to develop sort of the oversight that there needs to be over this area.

Bob Barrett: How can all of these new tests improve patient care?

Dr. Elizabeth Chao: So that's really the goal of genomic revolution, or even beginning the human genome project 15 years ago, even longer than that going back, is really to improve patient care and to approve patient health. And so being able to practice genomic medicine and to do this sort of testing, you really need to be able to apply, it's not just technology, but it's the technology that we want to use to answer a real clinical or a medical question that the physician is asking about their patients. And there are a couple of specific areas where this is more mature and I think there are other areas of medicine where it's just growing and we are just sort of learning how this sort of technology can improve patient care.

Bob Barrett: Well, aside from cancer and oncology, are there other applications for genomic testing today?

Dr. Elizabeth Chao: So, you mentioned two of the most common ones, doing cancer testing and looking at tumors, and sometimes even using genomic testing to guide therapeutic selection, to guide what treatment the patient is going to get is probably one of the largest growing areas.

But there are actually other areas where we are doing genomic testing that are even more advanced, so if you look at the area of rare heritable disease for example, and being able to use exome testing for example, for diagnostic

purposes, if you think about other medical specialties, neurology, where we have very good success in using this technology to diagnose, for example, seizure disorders, some of the causes of autism spectrum disorders, developmental delay, some of the really severe diseases and genotypes that present and often really we have never been able to determine a cause until today when we can apply this sort of genomic technology.

Bob Barrett: Will laboratories cope with privacy concerns, yet report and share patient genomic data?

Dr. Elizabeth Chao: So, that's a really interesting question and I think we are waiting to see how that comes out. There certainly is an effort to do that. So there is huge belief that by sharing data, we can improve the sort of testing and scientific understanding of this data, but how that's going to happen and how it's going to happen so that we are able to protect the privacy of patients is a big concern within the community.

Just recently the NIH actually released a report in the research space, basically requiring investigators to share genomic data and proposing mechanisms by which patients would be consented to that and sort of how it would happen. Dealing with genomic data in the clinical space is going to be an even touchier question, but I think it's inevitable and I think it will help the scientific community grow. I think it's more of a practical consideration right now about how and when it will happen.

Bob Barrett: Have they talked about patient privacy being protected with all that data being shared?

Dr. Elizabeth Chao: I think a lot of people are talking about it, but you know it's difficult. The approach in the past has been for the laboratories to collaborate and share what we call the de-identified patient information. So we might share the results of testing and maybe some of the clinical features of that patient, but wouldn't offer any identifying information about that patient, such as their name or date of birth and other things like that.

More recently people sequence a whole genome for example and then it bears the question, well how do you de-identify a genome when it really is a piece of identifying information? To date, it's nearly impossible to take whole genome sequence information and to infer some sort of identifying information out of that, but there have been proof of principle studies where investigators have basically used the internet and publically available resources to do things like that, which I think is a little bit scary to people when we talk about sharing genomic data. So there are

privacy concerns that will need be to addressed but I think that people are aware of the issues and they will be.

Bob Barrett: What about future discoveries? Now if a patient is tested today, how will their data be reviewed in the future in light of new information?

Dr. Elizabeth Chao: So this is a question we actually get all the time. You know people think about having genomic testing, I should get my genome sequenced, I should get my exome sequenced, but why would I do it know, won't we know more next year or in two years or in five years, so should I get it sequenced now? And we are thinking about that all the time.

So right now when you think about a clinical lab doing a genomic test, the vast proportion of the effort and sort of cost that goes into that is on the side of the analysis and interpretation, not really on the lab side. So when you think about reanalyzing or reinterpreting data, that's a significant proportion of the cost.

So that's something to think about and I don't think there are clear answers except that this issue is going to need to be addressed and different laboratories have set up different policies for data review. And I think right now a lot of it is at the request of the patient or the clinician, so a physician might call the laboratory back and ask for re-review because for example there has been some new clinical information that's come to light or the patients has gotten a new diagnosis which might allow you to look at the data in a new way.

And I think that's how it's most commonly proceeding right now, but it will probably become more systematic in the future.

Bob Barrett: Well, how often do you think that the data should be re-reviewed?

Dr. Elizabeth Chao: Well, at a first glance, I think it should be rereviewed anytime there is a significant change in the patient's health. So we are only as good at interpreting the genomic data as the clinical data, we have to go along with it. So anytime something new comes up, a new presentation, a new family member turns out to be affected that's going to allow us to really get a lot more, draw a lot more information out of the genomic data. So I think that's at a minimum.

But the truth is that, there are new papers coming out all the time identifying genes and we have had the experience here for example, of getting a diagnosis through exome sequencing based on a paper that was published in *Nature Genetics* last month and we think all the time, while when

we have a negative case, who knows if it's going to be the next month or the next year that that a gene might pop up. So I think that's a difficult question.

Bob Barrett: Well, the other question that's going to be asked is, is it going to be covered by insurance?

Dr. Elizabeth Chao: That's an even probably trickier question. So, right now the way clinical laboratories bill, most of at its basically based on the laboratory work and as I alluded to, that actually only accounts for a small proportion of the cost. So, if you send in a sample to have your patients exome or genome sequenced, then it takes six weeks for the analysis to come back, it didn't take six week to generate the sequence data, but a vast majority of that time was actually spent working on analysis and interpretation.

So right now, there really is no mechanism for this to be billed to insurance companies and covered, in terms of re-review. So my hope would be that that we will be able to address that situation and help payers to understand by doing rigorous scientific evaluation and producing the sorts of data that they would need to understand how important it is that somebody's cases be rereviewed.

Bob Barrett: Can—or maybe more importantly, should—the raw data be made available to patients or healthcare providers? Do the patients and their physicians really want to know more?

Dr. Elizabeth Chao: I think there are a lot of strong feelings about this that in general, the genomic data does belong to the patients. It is their genome. That being said most patients and even most healthcare providers are not really equipped to deal with the complexities of that sort of volume of information and possibly to learn more about it.

We do a lot of testing here, and we get a number of healthcare providers that actually do ask for the raw data back and we provide it to them. I think a more important question would be, you know what happens to it then? So we want to shipping at a hard drive with raw sequence data on it after we have already made our analysis and interpretation, and I'd be curious to know and hopefully, we will be getting data back, on what's the followup, how often does that actually turn out to be -- does the healthcare provider or the patient themselves find something useful on the data going forward?

So that would be interesting to know, but I think it really does pose a challenge to be confronted with that sort of data even if it does truly belong to the patient, what they can make out of it, sort of remains to be seen.

Bob Barrett: Dr. Elizabeth Chao is Director of Translational Medicine at Ambry Genetics. She has been our guest in this podcast from *Clinical Chemistry.*

I am Bob Barrett. Thanks for listening.