Clinical Laboratory Standard Setting
Carolyn Sue Richards, Ph.D.

DR. FERREIRA-GONZALEZ: Now we will turn to Dr. Sue Richards. Dr. Richards is a member of the Clinical and Laboratory Standards Institute, Molecular Area Committee, and a member of the CDC EGAPP Working Group. In addition, she's the chair of the Quality Assurance Committee of the American College of Medical Genetics. Her research interests include the transition of molecular tests from the research setting to the clinical setting, development of genetic testing for the rare genetic disorders, and interpretation of sequence variants. She's here to provide us with some insight on standard setting for clinical laboratories.

Dr. Richards?

DR. RICHARDS: Well, thank you very much for inviting me here to represent this area.

So while I'm involved in developing standards with a number of groups, I'm primarily going to be representing the American College of Medical Genetics in this talk, and then I will try to interface these various groups that are also involved in this big, important project.

So professional guidelines are very important to us for setting standards of practice. Through ACMG, there are multiple mechanisms by which we set professional guidelines. One is through the Laboratory Quality Assurance Committee and the other is through the Professional Practice and Guidelines Committee. And then we also have the mechanism of developing special projects of commissioned guidelines. And I will try to give you examples of all of these throughout the talk.

There are three different types of statements that may come from the college that would be viewed as practice guidelines or as standards: policy statements, in which this is often a response to a single issue that needs to be addressed immediately, and this is quite short. A practice guideline is generally a clinical guideline of how testing should be done in what setting. So this is talking to the clinical roles. Then accompanying that quite often is the laboratory standard and guideline, which addresses what I think we are addressing here in this meeting in terms of how exactly laboratories should perform particular tests.

So the purpose of our standards and guidelines, while these are voluntary, they provide an educational resource to primarily the laboratory, and we want to address the quality of genetic testing, ensure quality. And to that end, we actually address technologies and procedures in the clinical genetics laboratories in all of the subspecialties.

So I'm going to turn to the Quality Assurance Committee as a resource and how this is done. This group is dedicated to evaluating new technologies as they come in use in the laboratory, monitoring the accreditation requirements, as we've heard from New York State, from CLIA, and through CAP, and monitoring laboratory proficiency testing. We have on our committee representatives that attend these meetings for the CAP Resource Committee, and when these results come in, we want to know how laboratories are performing. We use these as triggers for developing new standards and guidelines. If there is an analyte in which laboratories are performing poorly, as we might have seen in test interpretation perhaps in the mid-1990s, then we address it with a guideline and we see the performance improve.

So our guidelines are virtually a notebook, a manual that continues to change over time with ongoing updates. We have what we initiated in 2000, the disease-specific guidelines, and I will

show you examples. We also are including model laboratory reports in our guidelines, and this is also very consistent with some of the other projects ongoing through CDC in looking at reporting issues.

We function as a resource for education, and that's not just for the genetics community, but we do outreach education. When we develop new guidelines, we try to be involved with different professional groups and organizations where we can go and give workshops and make the individuals aware who are actually performing testing that new guidelines exist because getting the message out is part of the issue. So that's to identify test quality and discuss communication of test results.

So who is involved? I tried to answer your who, what, and why questions. Who is involved in laboratory standard development? We have three working subcommittees from the Laboratory Quality Assurance Committee that addresses the basic issues of molecular, cytogenetic, and biochemical genetic groups. We have a biostatistician who is involved who helps to guide us in some of the validation questions and statistical work that we need to look at. And we frequently include experts in fields of selected topics that we are working on.

The current group is shown here. It's quite a large group, and it's composed of ABMG-certified clinical laboratory geneticists in these specific areas. We have representatives that are involved in the Clinical Laboratory Standards Institute, CLSI. We have representatives to CDC in working projects of EGAPP. We have representatives that are working with the CDC reports and how that's translated to physicians in communication efforts. And we have the CAP representative. So we have a pulse on what's going on in genetic testing, and we try to address new issues as they surface.

So just to recap, how do standards ensure quality of genetic testing? They set standard of practice in the field. They're used in developing the laboratory inspection checklists for CAP as a regulatory requirement for accreditation. And they're used in developing proficiency testing challenges and test interpretations through the CAP process and as an educational resource.

So I want to give you an example of how our private professional guidelines have intersected with government. I'm going to use an example that came out of a CDC and NIH-sponsored meeting that was in May of 2004, Promoting Quality Laboratory Testing for Rare Disease: Keys to Ensuring Quality of Genetic Testing. It was the first national meeting that would address quality and availability and accessibility of genetic testing for rare disorders. It was so successful that many more participants from many more venues came to the table in 2005. And as a result, this is where the CETT project, the Collaboration, Education, and Test Translation, came out of. But there were other products from that meeting that might not be recognized.

Now, this is the chart, diagram that I believe Marc Williams was referring to as our draft framework in the process to enhance genetic testing for rare diseases. Now, you will see that only as the government can do, it was quite a complex model. But I think what it illustrates is that there is so much room for interface with various organizations, professional organizations, government organizations, in translating potential tests into service in the end.

What I'd like for you to focus on is that there is a need for the guidelines and standards to ensure quality assurance for our genetic testing. This is where we feel that we play a big role in the development of these standards, and we want to work hand in hand with you.

So this is the other product that came out of that meeting. It was a laboratory guideline developed by the American College of Medical Genetics on technical standards and guidelines for molecular genetic testing for ultra-rare disorders. There was a need recognized for that guideline. I've listed here what the different sections address.

For example, technology guidelines, what types of technologies are specific for this type of testing, how personnel might need to be even more qualified in this area, how test validation should be done, quality control standards, and quality assurance programs that specifically apply to this type of testing, test interpretation, and so forth. We address pre-analytical, analytical, and post-analytical test issues. We even address pitfalls that could be involved in genetic testing to educate and make laboratories aware of this.

I'd just like to also reemphasize that we included sample laboratory reports in this document. We have had wonderful feedback from laboratories that this is very helpful to them both nationally and internationally. So I think this is an internationally recognized document, and it was published in Genetics in Medicine.

We have a number of guidelines that are being developed through various working groups, and this list here is shown for a number of documents recently that have come out of the Biochemical Genetics Work Group. You'll see that there are a number that are specific for prenatal screening. So a need was recognized here.

The same is true for molecular genetics disease-specific guidelines. Cystic fibrosis was a guideline, of course, that was prompted by the ACMG-ACOG recommendation to offer prenatal screening for cystic fibrosis to all reproductive couples. The technical guideline for laboratories came out shortly after that recommendation came through.

The Fragile X guideline was a guideline that was triggered because laboratories in the mid-1990s did not perform well on the Fragile X interpretation on the CAP proficiency test, and as a result of our guideline, they performed much better.

Cytogenetic guidelines are shown here. These are all approved guidelines. These are based on techniques and various tissue types that are examined whether prenatal or cancer. I'll just call to your attention we do have a recent guideline that has been approved by the board for comparative genomic hybridization, CGH, arrays. Hand in hand, that guideline goes with the practice guideline.

So not only are we developing other specialized guidelines in process, but we also have programs that we are launching through our committee to ensure quality of genetic testing.

What I'd like to call your attention to is the Quality Watch Program. It is a program for reporting and following up on adverse events that are suspected to be caused by laboratory products or reagents that would impede accuracy in genetic testing. This will be launched with our new website next month, and we're looking forward to a very interactive communication with laboratory groups.

So let me turn to how standard development is supported. Well, our committee from ACMG is comprised of volunteers. We all have day jobs. Commissioned documents that come from ACMG come through industry grant funding, and the cost of that can come at a very high price. For the pharmacogenetics standard and guideline that has been developed, it is estimated at

around $100,000 per standard and guideline. This covers meeting cost, evidence-based reviews, and administrative costs as well.

And our newborn screening documents -- and you might be aware of the ACT sheets that have come from ACMG. This was such a large meeting. The cost was closer to $1 million. So standard development does not come cheap.

How are standards developed? Well, first is to identify a need and to make sure that we want to move in that direction. Once there is a go-ahead, we identify a leader for the project who really is the one that is responsible for getting that written. But a work committee is assigned of approximately five or six members to accompany that leader. And through conference calls and emails, they develop documents.

Now, I'll just impress upon you that with all the standards and guidelines we have developed through this time, there are two meetings a year face to face, three-hour meetings. And the rest of the work is done behind the scenes, and there's no funding for it. So if we are lucky and we are fast-tracking a guideline, we can get a guideline reaching draft form within six months with a lot of work and commitment from those groups. And many guidelines take much longer than that.

There's a thorough review process for this, and we are trying to emulate the CLSI consensus document review. We're striving very hard to do that through review from the work groups, the committee we send out to experts in the field. We post the documents once we are happy with them on our website. We invite member comment. We take those comments to heart. We incorporate that back in. It finally goes to the board for approval, and then if it's passed, it is posted on the website, incorporated in the standards and guidelines and published in Genetics in Medicine.

And it doesn't end then. Let me impress upon you that there is a continual renewal, revision, and either we retire, we renew, or we revise at least every three years. So the more guidelines you get, the more work you have to do.

Are they enforced? Well, in our guidelines, we say they are completely voluntary. However, you have already heard that they're used for developing accreditation standards and proficiency testing models. So I would say, in fact, they are enforced through CAP.

How do they relate to regulatory requirements? We have higher standards. The requirements we put in our standards even exceed that of CLIA requirements. We have paid attention to CLIAC recommendations. We've incorporated them preemptively in our guidelines so that we would be very much on top of it. We reviewed New York State requirements. We include many of these in our guidelines. And we also interact with our European and Australasian counterparts to try to get some harmonization in the guidelines worldwide. We are very focused on looking at nomenclature standards and reporting standards.

So how do these standard-setting organizations interact with and involve the government? We do respond to the government on guidance statements and also on legislation proposals. Whether or not they want to hear from us, we do. We include government representatives in our committee work for developing the standards and guidelines. I'll just give you an example. We utilize documents that are produced through CDC through the ACCE review and now through the EGAPP process with evidence-based reviews that will be useful in our decisionmaking process. I've shown you the ultra-rare disorder example for that standard and guideline.

How do standards keep pace with advances in knowledge in technology? As I've told you, it is a three-year renewal cycle, but if things change before that time, we're quick to make changes in our documents. This is a very big challenge with very limited resources.

So just some facts to reflect on. We have a big job to do. There are a lot of genes, and there are a lot of diseases in which clinical testing is available and new tests coming on all the time. So when you ask me to address are there gaps in current standards, I couldn't stand here and tell you that there aren't. There will always be some kind of gaps. There are more genetic tests than we can develop disease-specific guidelines for, and our resources, of course, are limited here.

But I think there is a gap that perhaps this group might want to address and that is a gap that involves an area that you're actually going to be speaking about tomorrow, which is your gene patents and licenses. I think what is happening now is we are seeing, with exclusive licensure of testing to a single entity, that we will not be able to provide the expertise for developing the standards or the expertise for doing the proficiency testing or have the resources to be able to support that.

So are there opportunities for us to collaborate? Well, absolutely. We would welcome a collaborative effort with these groups.

We do think funding is a major message, that we could use help in funding for more guidelines development. We could actually have a full-time individual doing this and still have work to do.

But we think meetings that would bring groups together, similar to the rare disorder meeting, to discuss these areas and to give input from different stakeholders and interest groups and users would be a very good step, providing more funding for evidence-based reviews on genetic disorders, such as the EGAPP model, and providing funding for filling in the gaps. For example, one piece that's missing on our guidance document for pharmacogenetics is that we need randomized, controlled trials, and this is a huge undertaking to establish the clinical validation.

Just finally, do the laboratories follow the standards and guidelines? Well, we think that they do. The CAP surveys, as you have seen from Gail Vance, show that the laboratories who are participating in the survey are doing quite well. And we believe, since we are so connected with this survey and our guidelines are connected with it, that that means that they are using these guidelines.

This is a resource that I would encourage you to look at, if you are not familiar with the standards and guidelines. It is freely available to everyone. You don't have to belong to ACMG to get the standards and guidelines. Just go to the website.

Thank you.