Accreditation of Genetic Testing Laboratories
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DR. FERREIRA-GONZALEZ: Because of the time -- we're a little behind schedule -- we will have the next three presenters going back to back. So if you can write down your questions, and at the end of the three speakers, then we'll have the questions for all of them.

Now we will take a closer look at the role of the private sector organizations in oversight, beginning with the accreditation of genetic testing laboratories by the College of American Pathologists. Dr. Vance -- I'm not going to try to kill your first name -- is a professor of medical and molecular genetics and professor of pathology and laboratory medicine at the Indiana University, Kansas Center, and Director of the Cytogenetic Laboratory at the Indiana University School of Medicine. She's also a member of the Board of Directors of the College of American Pathologists. We are privileged to have her today discussing some of these issues. Dr. Vance?

DR. VANCE: Thank you for the opportunity to present the College of American Pathologists accreditation program this afternoon to you.

I need to explain to you that I have revised the order of the slides slightly. That is the blessing and also the curse of PowerPoint. So if you follow along with the slides, there will be a few that are out of order.

As a presentation of the overview that I'm going to discuss today, I'll discuss shared goals, the CAP accreditation program as it pertains, in particular, to molecular pathology and cytogenetics, the proficiency testing that CAP offers, and conclude with recommendations.

The goals of the CAP accreditation program, as I'm sure are the goals of this committee and other organizations, are to assure that tests being offered are analytically and clinically valid. We also wish to assure that there is patient safety and assure the public health and assure patient access to testing. We also wish to continue to allow for innovation and improvement of laboratory-developed tests.

The accreditation program is designed to assure that high complexity laboratory tests are provided by high quality labs that assure analytical and clinical validity of the tests they offer, that laboratories have a patient safety plan in place, and that there is incremental improvement and innovation in testing, and that that testing is not impeded.

Just a little bit of a background of the college. Now, as we are in the private organization session of the discussions, it is a professional organization. It's composed of approximately 16,000 board certified pathologists.

The CAP accreditation program is CMS-approved. It also, like New York, holds to a higher standard than the CLIA regs. We do have specialized inspector requirements for those inspectors inspecting genetics laboratories, and many of the standards that are created that are in addition to the CLIA standards arise through the scientists that populate the scientific resource committees.

In the College of American Pathologists, there are approximately 24 of these scientific resource committees. In the field of genetics, there are hybrid committees that are formed not only by college members who are pathologists, but also from laboratory scientists who are members of the American College of Medical Genetics. And you will hear from Sue Richards next who will be representing the ACMG.

Also, laboratories that are enrolled in the laboratory accreditation program are required to continuously report and update their testing menu. This serves for the purpose of not only knowing what they test for, but also so the CAP organization can match what the laboratory is testing for with the required PT.

A little bit of history about the CAP accreditation program. It began in 1961. It too predated CLIA. The program was initially voluntary. The first cytogenetics checklist and, therefore, inspections were offered in 1976, and 17 years later, a molecular pathology checklist was created and offered.

As a member of the accreditation program for the College of American Pathologists, laboratories are required to undergo biannual inspections. These inspections take place in the laboratory but by a team of external reviewers. So a team is formulated and they'll go to the hospital lab and inspect that laboratory. The team is usually composed of peer inspectors, and that means actively practicing scientists of the specialty which they're inspecting.

The tool that is utilized in these inspections is the checklist. Now, this checklist is not only a tool for the inspector, but it's also a tool for the laboratories so they understand the standards that they're being held to and they can utilize that checklist in preparing for their inspection.

There are approximately 18 checklists that CAP offers that consist of about 3,500 discipline-specific laboratory requirements. Over half of those requirements, approximately 1,700 questions, are in addition to the CLIA minimal standards. For example, there are special disciplines not covered by CLIA, and these include forensic testing, autopsy, histology processing, embryology, and also molecular pathology.

Sections within traditional disciplines that go beyond the CLIA standards include proficiency testing for nonregulated analytes, much like cytogenetics, laboratory computer systems, lab safety and hygiene, prenatal screening standards, and also sweat chloride testing standards.

As I said, the laboratories -- this includes the genetics laboratory -- are subject to inspection every two years. The inspection of the genetics laboratory requires special knowledge of the science. Therefore, inspectors are chosen because they are actively practicing molecular scientists familiar with the checklist that they will be utilizing and also possessing the technical and interpretive skills necessary to evaluate the quality of the laboratory's performance.

There is training for these inspectors. Training modules are offered as live inspector training seminars or online interactive training modules. There are also audio conferences that are created for discipline-specific areas.

Also, there are requirements now for the inspector team. As of July 2006, every team leader that takes out a team must have completed mandatory testing and then must renew that testing every two years. There is also training for team members, and regulations are being put into place for a requirement of retraining as well every two years.

Some of the standards that apply to genetics that, again, exceed CLIA are everything that's asterisked here. But we do include assay validation, as stipulated in CLIA, clinical validation, use of universal and proper nomenclature, correlation with clinical information and other studies, recommendations for genetic counseling and further studies, and turnaround time requirements. And I'll be giving you some examples of that in just a minute.

Other examples where the CAP standards are beyond CLIA will include, as an example, two of the questions from the molecular pathology checklist, such as, are the clinical performance characteristics of each assay documented using either literature citations or a summary of internal study results? Another: does the final report include an appropriate summary of the methods, the loci, or mutations tested, the analytical interpretation and the clinical interpretation, if appropriate?

The molecular checklist covers most aspects of clinical molecular testing, but as you'll see, it includes not only inherited genetic testing, but also acquired genetic testing in the form of oncology and hematology, infectious disease, also inherited disease, histocompatibility typing, forensics, and parentage applications. Any testing that involves DNA, RNA, or nucleic acid probe hybridization or amplification would constitute molecular testing, and that laboratory would then be inspected by the molecular pathology checklist.

Techniques are also covered within this checklist and include compliance with requirements for extraction and purification, amplification, restriction enzymes or endonucleases, sequencing, detection, real-time polymerase chain reaction, or PCR, arrays, and in situ hybridization.

And I will mention that -- Ann was just talking about arrays -- we are now piloting a test for the CGH arrays in the cytogenetics resource committees and hope to offer that as far as a proficiency test later on, but also in addition to that, we're setting standards for analytic and clinical validity, if we can, of the CGH arrays.

There's also a cytogenetics checklist that covers cytogenetic testing, both standard G-banding and molecular cytogenetics. This covers chromosome analysis of amniotic fluid and chorionic villi, non-neoplastic blood and fibroblasts, neoplastic blood and bone marrow. It also has to deal with the establishment and maintenance of cultures, cells counted, karyotypes, band levels of resolution, and as I stated, fluorescence in situ hybridization, or molecular cytogenetics.

So what happens if the laboratory conducts its business, abides by the standards, and is inspected? So at the time of inspection, what happens if the inspector sees that the laboratory is not in compliance with one of the checklist questions or standards? Then a deficiency is cited. And if that deficiency holds -- in other words, there is a discussion with the inspector of whether there is a deficiency or not -- and if the inspector decides that there is, in fact, a deficiency, the lab must respond with corrective action to CAP within 30 days of the onsite inspection.

After receiving the response from the laboratory, there is a two-tier review process. This is composed of both a staff analyst who's a technical staff analyst of CAP and also a practicing pathologist is designated as a regional commissioner to CAP. Between those two, they determine the adequacy of the action plan and the lab's ability to maintain sustained compliance. However, the ultimate authority or the ultimate decisionmaking resides with the Accreditation Committee of the Council on Accreditation. And this is a committee of lab experts who finally render their decision.

On an every other year cycle, in other words, on alternate years that the lab is not being externally inspected, the lab is required to complete a self-inspection and submit the results of that self-inspection. The results of that self-inspection then go into the inspector packet for the next cycle of external inspection. So that inspector will have with them the results of the self-inspection performed by that laboratory in the interim years.

Just to give you some information about how many labs that CAP accredits, we accredit both national and international labs. There's about a total of 6,600 laboratories that are accredited. Approximately 250 laboratories in the cytogenetics discipline and approximately 700 -- or that's sort of a dynamic number -- with molecular pathology discipline. As was quoted in Modern Health Care, this includes 98 of the top 100 hospitals, and the majority of large commercial reference labs, including Lab Corp and Quest, are accredited by the College of American Pathologists.

Some of the deficiencies that are cited after the inspection process in molecular pathology. There are three that are listed here, and associated with these, you can see the percent of that approximate number of 700 labs that were cited for this deficiency.

The first one reads, in the cases where there is no commercially or externally available PT, does the laboratory at least semi-annually -- that's in compliance with CLIA -- participate in external PT or exercise an alternate performance assessment system for determining the reliability of analytic testing? About 3.9 percent of the 700 or so laboratories received a deficiency for this. They must respond to CAP with an action plan in how to correct this deficiency.

Are temperatures checked and recorded appropriately for equipment in which the temperature is critical?

Is there a summary statement signed by the laboratory director or designee documenting review of validation studies and approval of the test for clinical use? And in this situation, there's about 3.3 percent of the molecular genetic testing labs that we accredit that have received a deficiency for this checklist question.

For cytogenetics, the most common deficiencies cited are: is the final report for tests requiring rapid reporting results available -- and that's the final report, not the preliminary report -- within 7 days of specimen receipt in at least 90 percent of the cases? And 7.6 percent of the laboratories inspected were cited for this deficiency.

Is the final report for neoplastic bloods and bone marrow analysis provided within 21 calendar days of specimen receipt in at least 90 percent of the cases? And 6.8 percent of the laboratories were cited for this. Again, this is a standard that goes beyond CLIA.

Are reagents and solutions properly labeled as applicable and appropriate? And there are four or five criteria that must be on the reagent that is being used. And if only one of those is missing, they are cited for a deficiency. And that's approximately 4.2 percent of the laboratories that were inspected.

So that's just an overview of the inspection process. I'd like to turn now to proficiency testing.

The college does offer external proficiency testing for genetic laboratories which allow the laboratories to regularly evaluate their performance and improve the accuracy of the results. In these proficiency tests, each laboratory is provided with unknown specimens for testing. They are told the category, but they're not told what particularly the specimen is. The participants analyze the specimens and return the results to CAP for evaluation. The results are evaluated by the scientific resource committees or their peer groups. And statistical support is provided by CAP.

So for these proficiency tests in genetics, to my knowledge CAP is one of, if not the only, very few that offer proficiency testing for genetic testing. Some of the products that are available include chromosomal abnormality identification, fluorescence in situ hybridization using chromosome-specific DNA probes, biochemical genetics for metabolic diseases, and molecular analysis of lymphoma and leukemia.

This is an algorithm that shows you what happens when there is a PT failure in a laboratory. This algorithm starts on the left with the black arrow. So the laboratory is required to participate in PT for its analytes. If it receives an unsatisfactory PT evaluation or one PT event, the laboratory is issued a warning for testing for that particular analyte. They're also provided with some educational material on how to do better.

They are then monitored. If they receive one unsatisfactory report of the next two PT events, they are given a choice to either cease testing for that analyte or to document a plan of corrective action.

If the laboratory chooses to document a corrective action plan, they submit that. It's reviewed. And if it's acceptable, they're allowed to continue testing for that analyte until the next PT event, and at maximum, that's six months.

If the next PT is satisfactory, then they are monitored again for another PT cycle. If they are good after PT cycle, they're allowed to continue testing, and they start the algorithm all over again.

If on the following PT event for that analyte, they again receive an unacceptable response, they are required to cease testing for that analyte, and then they must sign a cease testing form and then again document a plan of action to bring that analyte up. The earliest that that laboratory could be again testing for that analyte is approximately six months.

This just gives you a summary of some data. This actually is from the committee that Dr. Richards sits on. It's the Biochemical and Molecular Genetics Committee. It's a busy slide, so I'll go through it with you.

Down the left-hand side of this slide are the different analytes. So for the first one, it's Factor V Leiden. And there are two challenges. This is 2006A and 2006B. The number of labs that were tested for this analyte was 784. The number achieving a correct response for this analyte was 99.2 percent of the laboratories.

Right underneath that is the appropriate interpretation for the value that they discovered. For 2006 for A, there were 786 laboratories that participated in that PT, and 782 obtained the proper interpretation for that analyte, with a result of about 99.5 percent of the laboratories testing. And if you read across for the interpretation, the summary for both challenges A and B was 99.6.

I won't go through all the numbers, but I will read the different analytes that are on the left-hand side there so you understand some of the analytes that are being tested. So in addition to Factor V Leiden, there's prothrombin, prothrombin interpretation, methylene tetrahydrofolate reductase, Fragile X mental retardation, Prader-Willi, hemochromatosis, Duchenne's muscular dystrophy, and hemoglobins S and C. And as you can see, if you just look down the right-hand column there, laboratory performance on these various analytes was quite good in 2006.

So in conclusion, the CAP laboratory accreditation program we believe can serve as a model in your patchwork that you're designing to improve the quality of laboratory-developed tests through the accreditation process in a way that improves patient care, protects the public's health, but yet does not stifle or impede test development, innovation, and improvement.

Our recommendations to the committee are that private organizations, including the CAP, and laboratories should continue to build on the work with CLIA that has been successful, in our opinion, over the last 15 years. CAP also believes that the goal of assuring analytical and clinical validity for all high complexity laboratory tests can best be achieved through the CLIA inspection process. But we also understand and do realize that in order to achieve this goal, that statutory changes to CLIA may be needed.

And I guess I'll hold questions.

DR. FERREIRA-GONZALEZ: Thank you, Dr. Vance. This was an outstanding presentation.