AFTERNOON SESSION

Dr. Howell: Ladies and gentlemen, let's find our seats and move ahead with the program this afternoon. We still have a few folks who are not yet back from lunch but we are expecting a -- we have a quorum at the table and we'll proceed.

We're going to now move to a presentation by Dr. Carol Greene and Dr. Bin Chen who will present the Clinical Laboratory Improvement Advisory Committee recommendations for good laboratory practices for biochemical testing and newborn screening for inherited diseases.

The CDC is in the process of developing guidelines based on these CLIAC recommendations and is seeking input for this Committee for the purpose of developing a new MMWR guideline. Let me tell you specifically what the CDC has requested of this Committee.

The CDC is requesting consultation from this Committee in the following areas; considering the CLIAC recommendations are there CDC issues that should explain or clarify the newborn screening laboratory community or biochemical genetic testing laboratories in the upcoming MMWR document. What recommendations would this Committee provide.

Are there issues CDC should address in the MMWR guideline pertaining to newborn screening laboratory practices that were not addressed in the CLIAC recommendations and if so, can this

Committee provide recommendations in these areas.

Third, how should CDC encourage the implementation of the recommended practices once a perspective MMWR guideline is published. What efforts should be taken and who should be reached as partners or collaborators to help with these efforts? The current time line calls for a draft document to be ready for circulation to agencies, including HRSA, in September. And I might point out, this is September.

However, in order to provide additional time for our members to review the appropriate background that will be provided, the CDC proposes to fund a special meeting of the Committee by teleconference to obtain input from members provided the meeting can be convened in consultation before the end of October.

So I might point out, in your material on your thumb drive you have the CLIAC recommendations, which are considerable, and some of you I'm sure have thumbed through those. But we now will hear a succinct and thoughtful presentation from Drs. Greene and Chen.

Dr. Chen: Thank you Dr. Howell for the introduction. And I wanted to thank Dr. Michele Puryear and her office for giving us the opportunity to have this joint presentation with Dr. Greene. For our presentation I'll start with a very brief overview of the background information, how and what led to the

development of the CLIAC recommendations for good laboratory practice in biochemical genetic testing and newborn screening.

And then Dr. Greene will be discussing the CLIAC recommendations and their implications for newborn screening. Following that, I'd like to give an up date on the CDC effort to develop the good laboratory practice guidelines.

Now for those who are not so familiar with CLIAC, CLIAC is a federal advisory Committee that was established back in 1992. The mission of CLIAC is to provide scientific and technical advice to the government regarding clinical laboratory standards including clear regulations and their impact on medical and laboratory practice. CLIAC also provides recommendations regarding modifications needed to the CLIA regulations.

Just a brief overview of CLIA oversight for genetic testing. CLIA regulations apply to all patient testing preformed on U.S. patient specimens. Regarding genetic testing, there is a specialty of clinical cytogenetics and there are CLIA regulations right now for which there are specific quality control requirements and qualification requirements for the technical supervisors.

There are no specialty requirements for molecular or biochemical genetic testing because these tests are not considered a specialty or sub-specialty under CLIA. So these laboratories are subject to the general CLIA requirements for

testing and personnel requirements for high complexity testing.

Overall, CLIA regulations emphasize the analytical validity of a laboratory test rather than clinical validity and are not intended to address clinical utility. Since 1997 Federal agencies have been working with various advisory Committees and other stakeholders to consider quality assurance and oversight issues for genetic testing.

In 2007 CMS developed the action plan to enhance the oversight for genetic testing by providing guidance rather than prescriptive regulations. So in 2008 CLIAC provided recommendations for good laboratory practices in molecular genetic testing which were later included in the CDC and MMWR document.

This is what the CDC/MMWR document for molecular genetic testing looks like. I think it's helpful to show you what this document looks like because right now we're using this document as a model to help us develop the upcoming MMWR for biochemical genetic testing.

So I'd like to use this flow chart to give you an overview of the process that we are going through to develop the upcoming MMWR for biochemical genetic testing and newborn screening. So following the CLIAC recommendation to develop a separate guideline for biochemical genetic testing, CDC performed a gap and needs assessment which was followed by the formation of the

CLIAC workgroup.

The workgroup provided feedback input to CLIAC which helped CLIAC develop recommendations for good laboratory practice recommendations. So currently CDC is in the process of preparing the MMWR and is also seeking additional input to compliment the CLIAC recommendations. So that is where we are at this time.

Just to give you some additional information on the CDC assessment because we consider this a critical step in the whole process leading to the eventual publication of the MMWR. The CDC assessment served multiple purposes including data collection, gap identification, assessing the expertise needed for the CLIAC workgroup and also preparation of information and the resources to facilitate the workgroup evaluation.

Through the assessment we identified a long list of issue for the workgroup to discuss. Among those, one of the issues that we recognized was we also need -- we also need clarification regarding the scope of the future MMWR guideline because the existing definitions for biochemical genetic testing are quite variable some of which also have covered newborn screening.

So after we formed the workgroup one of the first issues we asked the workgroup to consider was to which tests and to which laboratories the future guidelines should apply. The workgroup

was formed in 2009 and worked very hard throughout the whole year.

The workgroup was chaired by Dr. Greene and it consisted of 13 experts representing broad perspectives relating to biochemical genetic testing and newborn screening. The charge of the workgroup was to suggest who the laboratory practices for CLIAC consideration based on the comprehensive evaluation of all the relevant laboratory standards and professional guidelines.

So this is just to give you an example to show you the depths and the breadth of how much information was reviewed by the workgroup to be able to generate the workgroup report. And I should say the workgroup -- the workgroup reviewed 19 comprehensive -- works just like this to formulate the workgroup report for -- that was reported at a February 2010 CLIAC meeting.

So at this meeting CLIAC reviewed the workgroup report and developed the full site of CLIAC recommendations that was -- that hopefully you all have had a chance to review before the meeting.

Now I'm turning this to Dr. Carol Greene.

Dr. Greene: And just so you have a sense of how much work the CDC staff did in advance with some help from CMS and some others, is that was -- that was one page out of six of a medium size one of those 19 documents that they prepared for us. So

thank you again to Michele and to the Committee for this opportunity.

And this is an overview, I'm going to walk through quickly the elements of the CLIAC's recommendation because we want to leave some time for discussion and I think we're going to be at one of the subCommittee meetings afterwards.

I'm going to focus as I go through this on what is most directly relevant to newborn screening. Of course in one sense it's all relevant to newborn screening because short term and long term follow-up involves laboratory testing for inborn errors of metabolism. But we'll focus on what's specific.

On scope and applicability, since newborn screening is biochemical genetic testing and could not be excluded from the scope of the document. There were some points at which this workgroup and therefore CLIAC, recognized the need to either point out some special issues.

So for example, in the recommendations there's a recommendation that blood spot samples should not be batched. And of course that's not -- that's relevant to newborn screening and not to other kinds of biochemical genetic testing and other places where CLIAC felt a need to recognize something that's distinct where newborn screening might be -- need to be treated separately or differently or as an exception. And that is that there might be State rules for consent for newborn screening and

have to defer to that.

With that said, again this is a beautiful slide that gives you a visual outline of how the recommendations relate to the total testing process and we'll walk through, again highlighting where there's something specific that this Committee might be interested in. But of course, as we get to discussion if there are things that I've skipped over that you've about and have questions, that's part of what we're here for.

So to start with, the recommendations address the types of information that should be available to -- made available from a laboratory to users of the laboratory. We want to be really clear, this is not prescriptive with respect to how that information should be made available.

But it's clear in the recommendations that some of the -- I should also say, it is clear in the recommendations that some information about testing is important for any kind of test like what kind of sample you should send and how you should send it.

And some information that needs to be available before testing is relevant only to certain kinds of testing. Like if you need to fast somebody or if it -- you know, how you need to grow skin cells and make sure that they're not contaminated. That's not relevant to all kinds of testing.

So this is an outline of what information should be made available by the laboratory in whatever means is appropriate to

make that information available and making sure that that is information appropriate to the specific testing.

Information that needs to be provided for each biochemical genetic test includes, for example, you'll find in the CLIAC document on -- in the clarification section for the information to be provided for each biochemical genetic test, a reference to an FDA guidance document titled Newborn Screening Test Systems for Amino Acids, Free Carnitine and Acylcarnitines using Tandem Mass Spectrometry regarding the definition of intended use.

Which in this case means the laboratory needs to make sure that users of the laboratory understand what is -- whether it's appropriate, whether it's an aniline in nucleic acid targets, specimen type, recommended patient population. What is ever appropriate for that test.

Continuing on in the pre-analytic phase of testing with respect to informed consent for biochemical genetic testing. So the CLIAC recognizes that very importantly and very strongly states that informed consent is an issue between health care providers and patients and families. That's not a responsibility of the laboratory. The laboratory may at the State level have responsibility for documenting informed consent.

So there's recognition that there are mandates at some -- in some states for some kinds of testing. But it's generally

not a laboratory responsibility. If the State is required -- if the State requires the laboratory to document consent, the CLIAC suggests that there should be a method for documenting that consent on a test requisition form. But again, strongly states that consent is an issue between health care provider and patient and not a laboratory issue.

For newborn screening of course there are special considerations. The CLIAC -- the workgroup was very pleased that the CLIAC agreed that in principle explicit written consent is not necessary for mandated public health newborn screening and -- but did affirm that consent will be appropriate for research uses.

Moving on to specimen handling submission and referral. Again, this is one of the places where newborn screening was -- got special mention as in do not batch the blood spots. I do want to highlight here this whole issue of the terminology of -- I put in "air quotes" here, unsatisfactory specimens.

This is a clarification of a CLIA requirement and this does not single out newborn screening. In fact, this discussion started around problems that arise when you have a critically ill child and the sample is sent for amino acids in a red instead of a green or a green instead of a red depending on what sample your laboratory prefers. Or if the sample is too small and the sample is technically labeled unsatisfactory but you

can't get another one and you need an emergency result.

And the point here is made in the CLIAC recommendations that there is an issue and they need to be very careful with terminology. If a sample is labeled unsatisfactory, you have to be clear if it's unsatisfactory for all purposes or some purposes and when you use terminology like unsatisfactory and then you get site visited by a CLIA inspector or a CMS inspector, then you are running an unsatisfactory sample. And that's actually a violation of CLIA.

So this is really to point out some important issues in terminology in this recommendations. And that's a term of art in newborn screening laboratories that the sample is unsatisfactory and we run it anyway. And this is really not to single out newborn screening, that's a point across all biochemical genetic testing when we're dealing with small samples and critical timing.

In the analytic phase, on page 11 of the CLIAC recommendations you'll find that CLIAC recognized that some elements of performance establish and verification are different when you compare diagnostic or confirmatory diagnostic testing compared with screening.

For example, in newborn screening he used the term cut-off which is just not a term that you will necessarily use in other laboratories. And so if you're -- when you're establishing your

performance characteristics in a newborn screening setting, you'll want to establish your cut-offs and make sure that people know what they are.

And again, this is not a set of recommendations that say what the cut-off should be or even look at individual tests. This is looking on principle and process stating that when you're in your analytic phase you need to be clear what your performance characteristics are.

Continuing in the analytic phase, control procedures. There were some really important issues here that took up a huge amount of time for the workgroup and the Federal agencies that had a lot to do with amino acid analyzers.

And actually newborn screening was in better shape then just about any other aspect of biochemical genetic testing and did not need any singling out there. Especially in proficiency testing. So newborn screening is actually doing better then much of the rest of the world in biochemical genetic test.

In test reports, the post-analytic phase, this is the first of three slides that I will not go through in detail but they're in your materials. Three slides that detail the recommendations for what should be included in a test report. If it has an asterisk, that's something that is included in CLIA but the CLIAC has now made recommendations for more -- additional or more specific information that should be included in the test

report for biochemical genetic testing.

This first slide focuses on processing including some discussion about retention. But there's more discussion of retention of samples and reports coming up. And here, let me just point out that in test report for example, CLIAC, CLIA regulations say that a test may be submitted -- a test report may be considered complete if it has the patient's name or some other unique identifier. For biochemical genetic testing the CLIAC recommendations say the report should include the patient's name and any other identifier but name is not an option.

Other things that you'll see for example here -- again, this is not intended to be completely prescriptive so that performance specifications and limitations when appropriate. Or here, that recommendations for consultation when indicated. Okay?

So again, a long list of things that CLIAC agrees should be on the test report. And again, this is to be appropriate to the kind being performed.

For the post-analytic phase retention of records CLIAC made a strong statement in support of retention of newborn screening samples and a strong statement of the need to be clear that QAQC is not a research use and that it is essential in the maintenance of quality newborn screening practices. And save

those samples for as long as you possibly can given issues of space and time and state law.

For personnel qualifications and personnel responsibilities, this is another area in which newborn screening was recognized to have some differences. So basically this follows for biochemical genetic testing laboratories and complex biochemical genetic testing, the diagnostic testing. It's intended to look quite similar to that for cytogenetics. But for newborn screening, recognizing that it's a different area with different skills we had some folks who are state health directors involved in this workgroup.

And you can see that the technical supervisor is where the expertise is. So lab director could be a lab director in name and the director of many, many laboratories. The technical supervisor is where you are sure that you have somebody who is knowledge who is actually running the laboratory.

And there it's -- this person CLIA requirements for high complexity testing, have four years of laboratory experience or training in newborn screening to be the technical supervisor. And if there's any CMS approved board certification they need to meet it and any other additional state requirements.

There were some CLIAC recommendations for issues to consider when introducing new testing. And you will find in the CLIAC recommendations that the special issues in newborn

screening specifically reference this Committee and its process for establishing whether something should be added to the newborn screening.

And quality management system is something that is threaded, is seen throughout the document. It's -- I'm not a laboratory person myself but those of you who are know that that's a more European approach to quality assurance in the laboratory and that it addresses some aspects of lab quality that are not traditionally addressed in this country that sort of follow the whole process and include more pre-analytical, post-analytical reporting and process. And the CLIAC recommendations suggest that we should be incorporating that into lab quality throughout all biochemical genetic testing and molecular and everything else.

Dr. Chen: Well it's hard to follow that. So that was the set of CLIAC recommendations that was made at the February 2010 CLIAC meeting. So following that meeting we in the CDC started the process to prepare the upcoming MMWR guideline. And we expect that this upcoming MMWR to serve major purposes.

One, to provide clarifications to applicable CLIA requirements to help laboratories preforming biochemical genetic testing and newborn screening to better meet these requirements and to provide guidance for quality assurance for those practice issues that have been identified as needing additional quality

assurance measures in addition to CLIA requirements.

So to make sure that the upcoming document will be comprehensive and useful to the community, we are soliciting additional input to complement the CLIAC recommendations in the upcoming document. We have obtained input from the Secretary's Advisory Committee for Genetic Health and Society. And now we're looking forward to the feedback from this Committee as well as from the Association of Public Health Laboratories.

So overall this upcoming MMWR together with the MMWR guideline for molecular genetic testing are intended to improve the quality of laboratory genetic services, enhance oversight for genetic testing under the current regulatory framework and improve health care outcomes for patients who receive genetic tests.

And this is the acknowledgment slide. It's very busy, it tells you how many people we should be thankful for including CLIAC, the two CLIAC workgroups and our CMS and FDA colleagues and the CDC team that put together the molecular document and is also putting together the upcoming molecular -- the upcoming biochemical and genetic, and newborn screening document.

So these are the issues that we would appreciate input from this Committee.

Dr. Howell: Thank you very much. I would -- one quick thing Carol is that I'm interested in the comment about a CMS

approved board certification. What does that mean? As far as I'm aware, CMS has nothing to do with board certification.

Dr. Greene: I think Bin can do that better than I can. And it's not that CMS approves the board, it's just that certain boards are named by CMS in -- certain boards are named in the CLIA regulations as appropriate boards for being a lab director.

Dr. Howell: So it's recognition of approved boards.

Dr. Greene: Yes.

Dr. Howell: Okay.

Dr. Greene: Yes.

Dr. Howell: The other thing is that I'm a little curious about how much involvement there is in these documents about informed consent. Because I'm not aware that the lab should be involved in informed consent.

Dr. Greene: The workgroup was very pleased that CLIA agreed that the lab should not be involved in informed consent. So the details of the document --

Dr. Howell: Right.

Dr. Greene: -- state that the informed, written informed consent is not the purview of a laboratory and the laboratory needs to make available to the people who might be involved in informed consent, sufficient information about the laboratory testing so that a discussion can be truly informed. So it is the responsibility of the laboratory -- if a laboratory is doing

a test that will tell you about your future health risks, then the laboratory needs to make available to the users of the test information about that test --

Dr. Howell: There's a problem with that, and that is that the lab doesn't order the test. The lab is ordered by a health care professional who would know the value of the test.

Dr. Greene: Okay, I --

Dr. Howell: So I think they need to get out of the loop.

Dr. Greene: I think I'm probably not making it clear. The health care professional, me for example as a physician, if the way that I learn about a test in order to know whether or not it's appropriate for my patient, one of the ways in which I learn about a test is by going to the laboratory site who offers the test.

And that laboratory site should make available information about the test, about the test limitations, about the background of the test so that I can make an informed decision about what I want to recommend.

Dr. Howell: Well that's seems reasonable. We have --

Dr. Greene: That is the purpose.

Dr. Howell: -- lots of comments.

Dr. Puryear: Can you go back to slide number 19 because that's unclear then.

Dr. Greene: And I want to say that we -- tremendous

appreciation for Bin. I apologize if I've left something unclear, but the work that went in to trying to condense this --

Dr. Howell: There you are.

Dr. Greene: If we've left something unclear I can also refer you to the appropriate page in the -- if the slide has left it unclear I apologize and the control information -- consent information is on page 5, begins in the document itself, in the CLIAC recommendations begins on page 5.

Most relevant is that we referenced the molecular recommendations in the MMWR that reads; all laboratory testing should be based on informed decision making. The laboratory should be responsible for providing its users with the information necessary for making informed decision and it should, the laboratory should be available to assist in determining the appropriate level of informed consent.

But informed consent is in the purview of the practice of medicine. The individual ordering a lab test should be responsible for obtaining the appropriate level of informed consent. It is not the laboratory's responsibility to obtain or require informed consent before performing the test unless state or local law mandates it. That's from the molecular MMWR that is also included in this recommendation.

Does that clarify?

Dr. Puryear: Well no, because -- it doesn't really because

of what you write here and what's on that slide.

Dr. Greene: Okay, what's on the slide, if it's not clear it is a paraphrase. The slide should absolutely should not trump what's in the document.

Dr. Puryear: Well I guess my question is, why should newborn screening even be mentioned since one, the newborn screening test is not ordered by the lab but in fact ordered by a health care provider in the hospital. And you seem to, in the CLIAC document characterize it, it's not necessary for mandated public health newborn screening.

It just shouldn't be a question I think for assays that are fully analytically and clinically validated. That the kinds of qualifications, again because the physician is ordering this it is really up to that physician whether or not that test meets your requirements I would think.

Dr. Greene: CLIAC has no requirements.

Dr. Puryear: But you've put lots of requirements in this.

Dr. Greene: The requirements are placed by this Committee. So if this Committee says it's a standard newborn screening then no consent is required. That is what CLIAC intended to say.

Dr. Puryear: But you didn't say that. You put lots of qualifications in A on -- I can't tell the page, page 6, lots of qualifications. But Mike Skeels was --

Dr. Howell: Mike Skeels and then Alan has -- Mike.

Dr. Skeels: I'm not sure if I was next. I had just sort of basic question. In addition to operating a CLIA certified lab I also administer the CLIA program in Oregon. And something we struggle with is trying to figure out whether given kind of laboratory testing like hair analysis or live cell analysis or you know, you name it, whether it falls under CLIA or not.

And I see danger here because my memory of the definition of a clinical laboratory test under CLIA is something like for the diagnosis, treatment, or assessment of health, right? So can you just say a little bit about where you draw the line between assessment of future health risk and assessment of health. And what will this apply to and what won't it apply to in the way of laboratory testing biochemical genetics? And feel free to talk about direct to consumer tests while you're at it.

Dr. Chen: The CLIA definition for a laboratory actually prescribes what laboratory and what kind of laboratory tests are subject to CLIA regulations. So in my view, assessing future health risks is also, is the same as assessing individual health risk. Whether the risk is current or future.

CLIA does not differentiate predictive testing versus diagnostic testing or screening testing as long as the test is performed for patient testing purposes for health assessment for modified treatment they are subject to CLIA regulations.

Dr. Skeels: Okay, thanks. So just to follow-up real

quickly. So since CLIA does not require that a licensed medical practitioner submit the sample some states, like my state does, but most states don't.

So if I'm hearing you right what that means is that there could be laboratories operated independent of the medical care system that fall under CLIA certification and could be operated completely outside of anything that's going on medically even though they're assessing health. Is that right?

Dr. Chen: It depends on where the laboratory is located. Because CLIA defers to law to determine authorize the person.

Dr. Skeels: And there's very few states left like Oregon that still require a licensed practitioner to submit a sample.

Dr. Chen: Yeah, right now based on the information we have at least 37 states allow direct to consumer testing to some extent.

Dr. Skeels: We're looking -- I'm in favor of economic development and I hope all of those labs will locate in Oregon but I don't think they're going to. So thanks.

Dr. Howell: Alan.

Dr. Fleischman: Yeah I just wanted to follow-up on some of Michele and Dr. Howell's concerns. There were two things carol that you mentioned and I think this was -- you know, it may well have been not in the document but in the way you paraphrased the document.

This morning we heard from Tracy Trotter that in California there's some kind of special process about the testing for SCID, that there's a special approach. Well this Committee has recommended that that be part of the core panel. And in fact, the Secretary seems to have accepted that recommendation and has deemed it such.

So I wouldn't want a laboratorian to think that you need some kind of special informed consent process for SCID today. Because it seems to be in -- well let me do the both and then you can go. It seems to be part of what we would consider a core panel.

Now if an individual state wants to do things well they're -- they'll be 52 or whatever flowers blooming. But I think it is important that the laboratorians know the complexity and the nuance of this problem. And that it not be simplified because they're important players in all of this.

The second was the comment you made about consent is appropriate for research uses. Well consent is certainly appropriate for some research uses and then there are other research uses -- I mean that's why we wrote that whole big document we argued about earlier in the day. Or at least part of why wrote it.

So I think it's important that the laboratorians understand that it's nuanced because they are asked by important decision

makers in the state for their thoughts, opinions and understanding. So that's the only reason why I think there's some little dissidence here.

Dr. Greene: And thank you and Bin is taking notes and she is very good at notes. So we'll be -- this discussion I think will help as the CDC prepares language and then routes it around for people to look at. I would start with your second comment and say that was clearly in excess of abbreviation in our preparation of the slide.

What the document says is any research use must be done with review of appropriate human subject's protection procedures. Which means you don't necessarily have to have consent if it's you know, normalized. So that was -- my apologies, that was too much short hand on the slide. We do not intend to say research only with consent.

Dr. Howell: This has been a very informative discussion. Let me tell you what, I'm going to ask our group to do. I would like to have you folks continue this discussion with Dr. Vockley who's chair of our Laboratory Standards and Procedure Committee.

And then if you can do that today Gerry during your meeting and come back specifically within your report tomorrow with a recommendation from this Committee about not only the document but whether or not you would feel it important and helpful to set up a conference call as has been suggested. And so if you

would assume that responsibility, that would be great.

Dr. Vockley: It's on our agenda.

Dr. Howell: Perfect.

Dr. Greene: And please, as you do that use the document not the slides. Because that was a perfect identification of a time where we, too much short hand on the slide.

Dr. Howell: Yeah, and we urge you to stay away from the informed consent as you probably heard. Thank you very much. We need to now try to stay on some schedule here. We need to hear now from Brad Therrell who's going to report on the HRSA-NNSGRC-APHL Hemoglobinopathy Workshop.

And folks around the group here know Brad who's the Director of the National Newborn Screening and Genetics Resource Center in Austin.

Dr. Therrell: Thank you Dr. Howell. Thank you Committee for having me give this little update. There was a meeting held a couple months ago as you've heard already this morning from Dr. Frempong and Dr. Cuthbert on hemoglobinopathies.

And the reason for that meeting was over the years as programs have evolved and there's been staff turnover, institutional memories have gotten rather short. And so people have sort of reverted to old habits and forgotten definitions and that sort of thing.

So we thought it would be nice to have a one day meeting

just to sort of reenergize the community and also to look at other issues that might be coming down the pike on their plates. And so we, from time to time have these issue and answer sessions. This one was co-sponsored with Association of Public Health Laboratories so there's both HRSA money and CDC money involved here.

So having the opportunity to give the first talk I thought I'd give you some of the slides that we looked at there. Just to ordinance you about newborn screening for hemoglobinopathies, this is a slide that shows you the different laboratory models that are being used in the country right now for newborn screening.

And that has specific impact on the various states that are using those laboratories as to what they do for their hemoglobinopathy testing. So those states that are the same color use a centralized laboratory that's shown by the star. Those states that remain in light blue all use their state public health laboratory. And so you can see there's about 8 or 10 different models that are being used.

Where that comes into play is in the next slide where we have shown you here in purple those states that use IEF, isoelectric focusing as the primary screening for hemoglobinopathies. And the light blue is those that use high performance liquid chromatography. And then there's one state

that uses both on every specimen, and that's Minnesota. So you can see again where the stars are and where the arrows are showing you what states send their samples to various laboratories.

Then because this community's been concerned with Hemoglobin H disease and that's more reasonably picked up right now by doing Bart's with HPLC technology, we asked the states who has capability to do HPLC right now. And so you can see those in green who now have HPLC available as a first or second tier.

So it wouldn't take much to get the rest of the country to have HPLC available. Whether or not they use it as a primary screen right now is another question. So there might be more money involved in those that don't use it as a primary screen. Or we need to validate IEF for that procedure.

We also wanted to know who's using DNA as a second tier. And so those states in purple or with purple slashes have some DNA available in their programs for hemoglobinopathies. Now let me just show you quickly the evolution of hemoglobinopathy screening over the years.

The first program was in New York in April 1975. And I'm going to give you 10 year increments. If you go 10 years forward to 1985 you see there were a few more states. And this is a mandate for universal hemoglobinopathy screening, okay?

If you go 10 years into the future you see that by 1995 almost everybody was doing it and that's because in the interim there NIH held a consensus conference and the results of that consensus conference were that everybody should be doing it. HRSA had some money available and they started putting it into grants and states began to do hemoglobinopathy screening.

So it very definitely depended on the availability of funds from the Federal Government to get those things moving. 2005, still a couple of states not mandating it. And I'm happy to say that by May 1, 2006 everybody had finally mandated it. So every state now mandates hemoglobinopathy screening.

Unknown Female Speaker: I thought it was 2008.

Dr. Therrell: 2006, but we can look later. It's either 2006 or 2008, but I think it's 2006. Okay, so just to sort of run through the program that we had so you'll get some feel for what was going on. We had Dr. Frempong give us a little hemoglobinopathy one-oh-one similar in some respects to what he did this morning.

And I've just got a couple of slides from him and I won't go through the details. But you can see the extent of the knowledge that was given to the participants was to look at little bit into the molecular technology available and the molecular understanding of the disease.

We got into definitions because one of the reasons we

wanted to have this meeting was because people seemed to have forgotten what definitions are. And so they call Sickle Cell Anemia Sickle Cell Disease for instance. So if you look to the right side of this slide you see the preferred acronyms right now so that you get the feel that Sickle Cell Disease actually covers more than just one disorder. And that was the point.

And it was interesting that after the meeting people came up and said, wow I'd like to be on the nomenclature Committee that's working on this because I've got a different way of defining that. And we said, well you know this has been done for years and years and years and that's why we had this meeting is to remind you that it had been there. So anyway, we had those kind of discussions.

We also got a little bit into Hemoglobin Bart's because not every state right now does Hemoglobin Bart's as you found out at your recent when we discussed Hemoglobin H disease and we thought this was a good opportunity to start educating people about Bart's and Hemoglobin H. And so you'll see some more slides as we go through this.

Carla Cuthbert came and gave us a review of what was going on at CDC and what some of the proficiency testing issues are. And she gave us the background of that program. And in your handout material we have put a paper in there which summarizes the background of hemoglobinopathy screening in the United

States over the years.

Interestingly she also showed us the results of the -- testing program by year. And you'll see that if you go down in the years the clinical assessment errors got smaller and smaller and smaller until all of a sudden last year it got larger. And so I called this morning to find out a little bit more about what was going on there.

And what this really emphasizes is the fact that CDC no longer has a pool of specimens from which to take their proficiency testing samples. They now have to do some individual samples and things like that. And this reflects some of the problem probably in developing those standards to go out. Not necessarily the laboratories although it could be the laboratories. So we've still got to look at this as we go through this year.

Looked at future directions at CDC and how it's expanding to meet the needs of other disorders as well. Then we looked at some examples of what state programs were doing. And so we had Texas give us a review of their program since they do IEF as a primary procedure and follow-up with HPLC and DNA. And so we had people from that program give a little bit of information about what's going on in Texas. Also, that's a laboratory that does second screenings on babies and so we had that issue as well.

California on the other hand uses HPLC in their contract laboratories and so we got the gist of how you do HPLC and what's going on in those laboratories from the California program. And because this is one of those procedures that's a little better at identifying Hemoglobin Bart's we began to get into the Bart's issue and the Hemoglobin H issue here.

Of course the California program is a little more complex then most and it's more the Cadillac of systems. And so we went into a little bit how that program's organized just to give people a feel for what they might be doing. I don't expect you to read this, just to note that it's a more disorganized or organized as you see it.

Cathy Hassel then gave us a little review of those non-targeted hemoglobinopathies that were detecting in programs and what's some of the challenges and considerations might be. And she has a term which I like called scope creep. So that we started off screening for Sickle Cell Anemia, we expanded that to Sickle Cell Disease and we've sort of crept into other things over the years as the procedures have picked up those other tests.

And so she talked about some of those issues particularly with regard to trait and how programs should be looking at trait and reporting trait and educating people about trait or carrier status as it's maybe better to call it.

Then we had Roger Eaton, and you heard about Roger this morning from Carla, talk about the issues in laboratory reporting and particularly is it possible for us to harmonize the way that 51 different programs in this country report their hemoglobinopathy results.

And so Roger went through and took a look at what the states are doing, in particular about 15 states as you saw this morning. And found out that you know, if we look at things there's a lot of codes out there that have been picked up in the standards but there's a lot more that might be being used.

About 270 were being used by states as opposed to 79 being reported in some of these codes. So this issue of what do we do with all these codes and do we really need all those codes and are some of those codes the same as other codes. And that's an issue that we're still dealing with.

And so for example, in the standard there's a term called Hemoglobin FA and other than, and it gives a bunch of different hemoglobins. But we don't have that for F, S, and variant hemoglobins and do we need that because other states are using that.

And so there were a lot of issues that came up there in terms of what different programs are doing that are sort of doing that are sort of non-standard and how we would go about standardizing that. And those issues are what Carla's going to

be dealing with with this hemoglobinopathy vocabulary Committee that she's talked about this morning.

Then we switched gears and got into Hemoglobin H. We had Elliott Vichinsky give us an introduction to Hemoglobin H and epidemiology and the natural history. And this was sort of new information for most people at the meeting. That was followed-up by one of his colleagues talking about observations during childhood, particularly in a California program with Hemoglobin H.

We looked at the Thalassemias screening program in California as well because most programs don't target Thalassemias in the way that California does. And if we're going to get into Hemoglobin H these issues about Thalassemia are going to come up. And so Fred Lorey gave us a talk about that.

And that was followed with Carolyn Hoppe, who was by the way the host for this meeting at the Children's Hospital in Oakland, giving us a little bit more information about how they do the confirmatory testing and follow-up in California.

I believe that's -- oh yeah, and then Dr. Frempong gave the participants a review of the information that had come from this Committee on the evidence review of Hemoglobin H so that they would know what the issues were that were going to be answered in the next few months.

So that's sort of the gist of what the program was. It started at 8:00 in the morning and it went until about 4:00 in the afternoon. We were expecting about 35 people because it was a relatively short notice meeting. We ended up with 60 participants. So we had a full room and it was well worth the effort of putting it together I think.

In the end we were able I think effectively to update and educate the program staff that were there. We got volunteers who were willing to work on the vocabulary issues that were pointed out. And we got a lot of recognition about what the Hemoglobin H issues are and where we might be going in the future.

So in a nutshell, that's what we did in that day and that's for your information.

Dr. Howell: Brad, thank you very much. Are there questions or comments for Dr. Therrell?

[No response.]

Dr. Howell: Sounds like a very good workshop. Unless there are no further discussions we are now going to adjourn to our Committee meetings, subCommittee meetings. The Follow-up and Treatment SubCommittee will be meeting in this room. So as soon as the group disperses we can convene back here.

The Laboratory Standards and Procedures are meeting in Salon 1, which is on the second floor. The Education and

Training is meeting in Salon 3, which is also on the second floor. And following the subCommittee meetings we will adjourn for the day.

However, the Health Information Technology Workgroup will not adjourn but will start their meeting at 5:15 to 6:30 and it again will be in Salon 1 on the second floor. It will be in the same room in which the Laboratory Standards and so forth.

And then we will reconvene in the morning. We've got a busy morning tomorrow. We've got a lot of exciting things to deal with. We'll start off with the review of the subCommittees and then the congenital heart disease issue and so forth.

Thank you very much.

[Whereupon, at 2:00 p.m., the afternoon session was concluded.]