Transcript: Friday – September 20

Morning Session

Thank you very much for standing by. Please continue to hold. Conference will begin in about two more minutes. Again, we hope to begin at five after. Please stand by.

Thank you everyone for standing by. Now at this time, all participants are in a listen-only mode. To ask a question during the question and answer session later, please press star then 1 on your touch-tone phone. Now I'd like to turn the call over to Dr. Bocchini. Sir, you may begin.

Thank you. Good morning, and I want to welcome all of you back to the second meeting of the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. This is Day 2 of this meeting. We just have a couple of housekeeping notes and reminders for the committee members. Please keep conversations and background noise to a minimum. The microphones in the room will transmittal sounds within this room. And when speaking please state your name each time. Also please speak clearly to insure proper recording for the transcript and the minutes. For the public, just a reminder that your sound will be coming through your computer speakers, so please make sure you have your computer speakers on. I'll start the meeting, we will conduct a roll call. So we will go again alphabetical order. Don Bailey?

Here.

Jeff Botkin?

Here.

Coleen Boyle?

Here.

Denise Dougherty?

Here.

Charles Homer?

Here.

Kellie Kelm?

Here.

Fred Lorey? Fred's not here yet.

For Michael Lu, substituting for him – Chris DeGraw?

Here.

Steve McDonough?

Here.

Dietrich Matern?

Here.

Melissa Parisi?

Here.

Alexis Thompson is unable to be here today. Catherine Wicklund?

Here.

Andrea Williams?

Here.

Debi Sarkar?

Here.

Now for organizational representatives, for the American Academy of Pediatrics, Beth Tarini?

Here.

Michael Watson, American College of Medical Genetics?

Here.

Mindy Saraco from ACOG?
Association of Maternal and Child Health Programs, Carolyn Mullen or Kate Taft?
Okay, Association of Public Health Laboratories Susan Tanksley?

Here.

Association of State and Territorial Health Officials, Chris Kus?

Here.

Department of Defense Adam Kanis?

Here.

Genetic Alliance, Natasha Bonhomme?

Here.

National Society of Genetic Counselors, Cate Vockley?

Here.

And Society for Inherited Metabolic Disorders, Carol Greene?

Here.

Okay, thank you very much. For this next session, we're going to hear the reports of each of the three subcommittees, and what we would like to hear is an update on the current priorities and projects, and then if there was some discussion about the future potential projects that you'd like to bring forward to the committee for its deliberation and recommendations, we would like to hear those as well. So we're going to start off with the subcommittee on Laboratory Standards and Procedures and we will look to Kellie or Susan to present. Kellie?

Good morning. You need to get to a microphone.

Oh, okay.

Good morning.

Okay.

[LAUGHTER]

So Susan and I are now chairs/co-chairs of the Lab Standards Procedures since Fred is enjoying his time at the beach, and although he is still coming, and lending all of his knowledge to our group. So we had a very interesting and provocative meeting yesterday. Next slide.

So here is our existing list of priorities and some of the projects that we discussed yesterday. So priority A is a review of new enabling and/or disruptive technologies and actually, we talked at great length, and I'll be talking about that here in a bit, about the succinylacetone

implementation survey which is not new, enabling or disruptive, but actually just revisiting sort of an issue and we gathered some information on that to share.

Priority B provides guidance for State programs and making decisions about labs implementation, integration, follow-up and Quality Assurance. We had a brief update from Amy Brower on the SCID slide deck, and from Jelili on an APHL update on NewSTEPs. And our last priority is establish a process for regular review and revision of the Recommended Uniform Screening Panel in coordination and collaboration with the other subcommittees but we have no projects under this priority at this time. So we are moving to the next slide.

So here, we had a probably about one hour, very interesting presentation discussion on the Succinylacetone (SUAC) implementation survey, and Carla Cuthbert and Victor DeJesus and Dieter Matern provided us this great update on, I can tell you about you know what we, some of the results and talk about future steps with the survey.

So briefly, Tyrosine is not a specific marker for TYR Type I. It's also elevated in other forms of Tyrosinemia (TYR)as well as some other conditions, so SUAC is a specific marker for TYR Type I, but it was not detected by routine newborn screening.

Here is the current status of the states, and what the blue states are states that still use Tyrosine as their primary marker for screening of this condition, the yellow overwhelmingly are states that use SUAC, and the orange use, they used Tyrosine as a primary marker and SUAC as a secondary marker, so there was interest in sort of exploring the difference between the states and what barriers for the states that still use Tyrosine in moving to SUAC because of this issue we know about Tyrosine as a marker, so they will talk a little bit about that survey.

So the response, so if I recall Carla said they started with a very smaller survey and then they got permission to expand it, so they actually contacted all and got a response from 31 out of 38 laboratories that they reached out to, and this is only domestic programs, even though we know CDC for example, works with international groups, and this survey results will be based on 16 states that do use SUAC and the 15 remaining states that do not. And there were different sets of survey answers for whether or not you answered yes or no, so there wasn't the same exact answer for both groups, and mainly we were focusing our discussion on the group that said no, they haven't and what their barriers were. So, next slide.

So I didn't present a lot of the data here, just some of the take home messages, so obviously, screening for TYR type I should remain. That's really not in question, so right now all of the U.S. programs do screen for this condition. The other thing that we had a lot of presentation on was the CDC's QA/QC and proficiency testing program that includes this condition and also the data they've gotten for the labs that use SUAC, so we actually saw a lot of differences and talked about the difference between people that use derivatized versus non-derivatized methods and those that use kits versus non-kits, and we also briefly looked at some of Dieter's data and how that might impact for example, CDC considering adding some samples not just around the cutoff but above where you actually might find just above the cutoff where you find some

affected baby samples come out, so we have the three bullets sort of the take home message from the labs that are not adding SUAC to their programs. So several of the labs indicated a strong pushback on adding SUAC because of limitations of the kit that are available. The other barriers that were named, generally equally, was funding issue, infrastructure, staff, technical expertise, but there really wasn't any one overwhelming barrier. It appeared that states named for adding it or not adding it, maybe it would add to the kit, that there was several comments in the open comment text box section on the kit.

So one of the questions that was asked was, would a recommendation from this committee influence their program to adopt SUAC, and the separate question was whether or not a recommendation from the Secretary would influence their program to add it, and in both cases, eight out of 15 of the states said that the recommendations in this body or the Secretary wouldn't influence their programs, although four said that it would and three just said not applicable which I'm not sure, we're not sure what that means. So although it's not necessarily a majority, it's sort of 50/50 that said no, it wouldn't mean much. So that's sort of where we are, so I think the update was that in the next few months that the group plans on putting together a publication to submit for, to publish the results, and I think we hadn't decided, we were going to have to see what the product is and see what they would like in terms of some movement from this committee, or just if it's information from the committee, so we'll have to see what as they move towards writing those, if the results are in, what's the final product and what our groups will be doing. So it was very informative and I thank that group for sharing. And I think the only other question that we did discuss briefly, you know, I know Susan and I were talking about, obviously this group only recommends that a condition be added to the panel and even though we sort of got a 50/50 answer on whether or not this group would recommend, should recommend for example, SUAC, we're talking about whether or not it would be something important for this group to make some sort of a recommendation about adding SUAC, and if we really think that is an important improvement or step that labs should take.

So then we had a series of updates from a lot of the groups that are doing some of the other projects. Next slide.

So we got a brief update from Amy Brower on the SCID slide deck and they still have monthly calls ongoing. We don't have a slide deck to present at this time, so this is the slide deck that was proposed that would actually be for, to present to the decision makers in states in order to encourage them to consider helping the labs add SCIDs. So whether or not the labs may be interested doing it but providing some information that would help the decision makers, be encouraged to add SCID and provide funding for the states to add it, and obviously we thought that we would start with SCID, and this could be a good template in case we wanted to see this for other conditions we add to the RUSP, whether or not in the future. Jelili and company from APHL gave an update on all of the activities that they've been involved in so first there was, of course, a number of us has been involved in the 50 year screening celebration and activities that have been going on the last week and more, so they talked briefly about some of the lobbying and celebrations and awards and I know everyone was interested, so we got a brief

update also on NewSTEPs, so there has already been some new updates for the website and some that will be coming up soon and that was going to include the list of case definitions and quality indicators as well as I actually looked last night at some of the new State profiles that are available, and the big item that they are currently working on is MOUs with states on moving forward within the future on data collection for getting those in place, and obviously there may be a lot of differences between states on what they can or are allowed to, so that's hopefully, I don't think it will be a small issue and we'll see what happens there. So Jelili also said that APHL would shortly be starting on the public health impact review of MPS 1, that's needed for that condition when it would be presented to our committee for consideration, and last that they would shortly be starting on a survey of states to assess the implementation and use of the recommendations in the CDC and MMWR on biochemical genetic testing that I think has been presented to this group or the subcommittee at least two or three times in the past.

And we also got a general update from Harry Hannon and Bob both, so first update they provided was a new standing subcommittee that was formed and, as you can see, it sort of in a parallel pathway from what is currently used for development committees so this is going to, they felt this was needed to get some of the documents moving a little faster, so the subcommittee that will review proposals and then based on those recommendations, working groups will be formed to actually start to write the documents and hopefully get them moving quicker than what we've been doing in the past, although SCID was a year, I think we talked about that was pretty good.

The other thing we discussed was the fact that there has been a change in the nomenclature, so now we have this new special designation for the newborn screening documents, and so NBS Number 1 is blood collection of filter paper and you can see a number of other ones that have been issued have also been reassigned new numbers, and the one that is currently under process just started earlier last week as NBS7, Newborn Blood Spot Screening for Pompe Disease by Lysosomal Acid Alpha-Glucosidase Activity Assays, so the original proposal was for a more general lysosomal disorder type document but I think that the group decided to focus it on Pompe Disease specifically, so that is under way right now, and the other important project that is coming soon is a work group that would be talking about terminology harmonization that could be used for all of the newborn screenings documents going forward, although it didn't sound like it was going to be setting a set of terminology and never changing then. It would always be open for comment and that work groups could always sort of go back and discuss if there were any new comments or concerns with some terminologies that the CLSI documents would be using. But I do think, having worked on some of these, if there was some set ahead for the terminology it would probably reduce some of the time that the groups spend on discussing terminology with every document. Next slide.

So I'll just say that we did briefly discuss Bob's talk a little bit, about the group that the working on the Pompe document, and we had a little bit of an outline that talked about it but it's going to be a lot like the SCID document, in providing some information to the states or anybody who wants to start a program on the different methods and obviously things that they should think about when setting up a Pompe screening program. So any questions?

Kelly, thank you very much for that report. Yes, let's go ahead and start.

Please identify.

Denise Dougherty. So, one question about the public health impact review, well two questions actually. One is, and forgive me for not remembering, but does this committee have a template or guidance to guide those public health impact analysis that everybody would use and just the way that we've developed?

[INAUDIBLE].

And then the other question is how long does it take to do a public health impact. I guess it could take as long as you have, since you keep digging and digging and calling people for information.

Without ruining anything for this afternoon and giving away the excitement, I think that it depends on what the questions are that are important to move forward [INAUDIBLE].

I'm sorry, we can't hear you.

I wasn't saying anything important anyway.

He wasn't talking to the microphone. The public didn't hear that.

This is Alex Kemper. I said that it's excellent question of the public health impact has meant and what I'd like you to do this afternoon is readdress that in terms of considering what are the really important questions and we'll be able to resolve these issues.

And just to emphasize?

Into the microphone.

Just to emphasize, we need public health people on that group, to do that assessment?

Yes.

[LAUGHTER]

You know, I forgot to come back--

[LAUGHTER]

We did start talking and brainstorming some future new projects but right now, we didn't actually have any focus, we're going to have to continue to work on coming up with some focus proposals that we think our group could answer. We had a number of sort of brainstorms and had a number of proposals and I think we're going to have to do some follow-up emails and meetings to actually narrow down to a question and something that the group can actually do, some of the questions were rather large.

Can I ask Carla, at one point when we were talking about Tyrosine and making changes, the CDC was thinking about an MMWR publication related to how laboratories were doing and some recommendations. Does that dove tail with what we just heard from the subcommittee?

[Inaudible] …whether or not it will be a MMWR publication or some other publication [inaudible]

Okay. Thank you.

All right. Additional questions or comments? If not, thank you very much for an excellent report. Next is the report from the Subcommittee on Education and Training. Don Bailey will make this presentation. He's the chair of this committee.

[Indiscernible-low volume]

Good morning everyone. How's that? [Laughter] I will back up a little bit. So, speaking on behalf of Beth Tarini, my co-chair, and all the committee members, we had a great eating yesterday. We will give you highlights from that. Next slide, please?

So, just in general, as I always do, I remind you of our charge, review of existing educational and training resources, gaps, make recommendations for a variety of groups. It's a very broad mandate work. Next slide.

A great group of members from both the committee, the organizational reps, and a number of key consultant members. Just to say that our committee meetings must generate a lot of interest from the public or other advocacy groups. I think we had 26 or 27 people that also logged in on the line. So, we do talk about things that are of direct relationship to many of the parent groups. Next slide please.

We have three priorities. The first is to promote newborn screening awareness among public professionals. Only a brief report here, current activities have been to divide support and input on the 2013 newborn screening awareness campaign activities. We had some slides from Carla and Jelili about a variety of activities that you heard about before, about the 50th anniversary celebration. I won't belabor that today. We do know one of our goals is to identify ongoing strategies for newborn screening awareness after 2013. We really didn't get a chance to talk about that very much in this meeting. I did have an off-line conversation with Carla and she

assured me that CDC and APHL are not stopping at the end of 2013, and thinking about other activities. We definitely want to be coordinating with those groups. Next slide, please.

So, you've seen this already. I won't stick with this slide long. Just a variety of activities that have happened over the past year, and I think we should all express our appreciation, both to the CDC and APHL, a strong set of awareness activities ranging from Times Square to a variety of other things. It's been great and now we just need to keep the momentum going. Next slide, please.

Again, the big question now we have to address is what should be the focus of our post-campaign awareness activities, and we will need some input from this broader committee, in terms of what you think might be appropriate activities. If you have time and have input today, we can have a discussion at the end. Otherwise, we will put that on our agenda for the next meeting. Next slide, please.

The second priority is to provide better guidance for advocacy groups and others regarding the nomination and review process. This came out of a lot of discussions we had about, maybe a lack of clarity for some of the nominators about different components of the review process and what was expected. What we wanted to have, was a document that would clearly enable successful applications. The original project was to develop public-friendly summaries of previously conducted evidence reviews, as well as evidence review nominations that have not gone forward. This original thinking I shared would be to talk about lessons learned from prior activities. That was going to be the key focus of this document. We realized halfway through that that we have a problem. The nomination and review process has really evolved since this committee was first formed. The lessons learned from the earlier failures might not be as helpful as something that might be a more forward-looking document, based on the current framework and footprints that have under current guidelines. We have -- we had a mid-course correction this summer with the project, to focus on the goal of developing a public-friendly summary of the nomination and review process, itself, where we are right now, as opposed to why things didn't happen in the past. We'll still be reviewing some of those earlier ones and looking with lessons learned, we might be able to include in this document. We've reframed the focus. The goal is to support return nominators and preparing a successful application practice. Next slide, please.

The original timeline was, last year we presented this idea. You supported it. We framed it up. Then, HRSA contracted with Atlas Research to do some draft documents. They were reviewing the prior letters that went out for the various nominations in the past. They developed some documents and we were going to review them and give you a report, today. We are not going to do that, because we had this mid-course correction. Next slide, please.

The revised activity, Atlas was asked to, first of all, interview experts closely associated with the committee and familiar with the review process. Then, to review the existing framework and guidance documents, to prepare a snapshot summary document based on this review and on the interviews. Next slide, please.

Here's a list of the experts that were interviewed and these are primarily either members of the committee or organizational reps or people who have been heavily involved in the condition review process.

These interviews focused around a number of key questions. What did each of these people think were the factors and priorities guiding the committee? What do they think about the relative importance, how strongly did the personal stories played in the nomination package and decisions. The importance of the overall package, the decision matrix, the condition review process, the importance of the lab tests and how the committee evaluates the state capabilities as related to the question we just had about public health impact. The importance of sufficient, high quality data. What did we mean by that? Did you always have to have a perfect gold standard study? Or was it more accumulation of types of evidence. Understanding what the definition of treatment is. How important it is to involve a variety of disciplines and advocacy organizations and, then, what resources did these experts recommend be available for nominators? Next slide, please.

So, our revised timeline, so, Atlas did these interviews this summer and prepare draft documents for us, which we received last week and we reviewed and discussed in our meeting yesterday. Our summary conclusion is that this was a good start. But, it was still not in the form or completeness that we wanted yet. One of the main things missing from that was interviews with advocates and nominators and professionals who might've been affiliated with some of those nominations. Atlas has agreed to do that very quickly for us over the next couple of weeks and provide transcripts of those. Their work will be ending at the end of September and this will be turned over to the subcommittee for next steps. We have taken it on, now, to take this body of information that's been gathered and to, now, write a document we think will be appropriate. So, we have asked for volunteers in the subcommittee, immediately six people raise their hands. There's a lot of interest in this. We have a great group of people willing to jump in on this. I think it's going to be a collaboration among people from the various organizations, as well as researchers. Our goal is to have a back and forth on this document over the fall so that's an error on the slide. It says September 2014 draft. It should be January. Our goal is to have this for you by the next meeting. Next slide, please.

Our third activity has been -- the real priority is to provide input on facilitation of national education and training initiatives. We interpreted that broadly and have taken a project of identifying – originally, to identify one period of a condition not part of the RUSP, but for which screening and treatment most likely would occur at a later point in child development. Think about the major education and training needs for that condition. Again, we are the Discretionary Advisory Committee on Heritable Disorders in Newborns and Children. So, this is the children part of this. What would be things we would do outside of the newborn period, which is obviously a huge challenge. Next slide, please.

In our January 2013 meeting, we selected -- we decided that one condition wouldn't be sufficient for us. Things are so different and this is a lesson we are learning already, that the

decisions and recommendations might be very different by condition. We took three exemplar conditions, fragile X syndrome, long QT syndrome and Wilson's disease. There's a big long validation process and thinking about what might be exemplars. These are. We think they are, necessarily, really the ones that are most ready for prime time for some of the kind of decisions we think that would help facilitate our discussion.

In the May meeting, we, I did a presentation on fragile X syndrome and in our meeting yesterday, Beth organized a presentation on long QT syndrome. In January we hope to get Pierre Ronaldo to talk to us about Wilson's disease. Then, we will reflect on all of this and have some kind of report to you in May. This is – sometimes, it can draw a direct line between what you thought you are going to do and what the ultimate outcome will be. This is more of an exploratory project. We don't know where the path is going to lead us on this. The two presentations already have been extremely interesting and had a lot of good discussion. Next slide, please.

Here other questions that we are asking ourselves in general about each condition. First of all, what is a typical pattern of identification of children with this condition? The average age of identification. For example, last time when I talked about fragile X condition, the average age is about 36 months. What are the problems with that current pattern of identification? What is the cost to children or families or society? And problems that could be ameliorated to some extent by earlier identification? So, for example, with fragile X, the problems are – kids could have entered earlier intervention programs much earlier. About 30% of families have a second child with fragile X syndrome before the first child is diagnosed. That is showing you what we are learning as we go through this process.

Thirdly, what populations screened outside the newborn period would be feasible or desirable? This is a huge challenge. The newborn period -- everybody gets screened. There really isn't another time that everyone gets screened for something that we've had in the later period. This will be a challenge for us. Then, in the absence of population screening, what would be the likely best case scenario for earlier identification? For fragile X, I laid out a scenario where the best case scenario without population screening would probably be around 12, 16 months of age. That would still miss a lot of children. So, if we did that, what level of effort would be required to substantially change the current paradigm from minimal to heroic? I would say for fragile X and now long QT, both are heroic. These will be interesting and important challenges for discussion, not only stakeholder groups that need to be engaged in these discussions about altering current practice. Next slide, please.

Beth did a great job of presenting about long QT syndrome. I'm going to very quickly highlight some things in her slide. I may not pronounce all the words correctly. I'm not a physician and I'll rely on Beth for the high points. Long QT is an inherited genetic channelopathy. It's identified with ECG. The cause is -- you have an increased propensity for a variety of different outcomes — the worst of which, of course, is sudden arrhythmic death. At least for what we know, five genes make up the classic form of LQTS, but there are 300 different related mutations identified on those genes. It would be a complex genetic testing paradigm. Next slide, please.

Estimated prevalence is about one in 5,000, an Italian study of neonates prevalence of one in 2,500. These were once what symptoms based on the ECG, so we don't know if they really have the disease or not. It's a question we will come back to a minute. Clearly, as variable presentation influenced by a variety of factors, including age. Next slide please.

So, what it is identified, it can be treated through beta blockers as a first-line prophylactic therapy. The initiation of treatment is dependent on clinical risk. The clinical risk isn't always easy to determine. Also, implantable cardioverter defibrillator is a secondary intervention strategy in high-risk patients. Next slide, please.

The typical patterns of identification could be through ECG and clinical history. But, there is a scoring system that can be used in cases. Currently, genetic testing is used largely for research and not clinical identification. That identifies about 75% of individuals with symptomatic LQTS. There's good specificity but not very good sensitivity. Next slide.

So, in terms of clinical presentations, there are a variety of different things that could trigger a question about, whether it's a child or an adult that has the syndrome. If you have this syncopal event, it could be an unexplained sudden death in a young individual. Family history, a variety of different pathways to identification. Next slide, please.

What problems exist with the current pattern of identification? There is one big one; we know that first presentation can be sudden death. So, ideally, if you could have some kind of screening program to prevent a death, that would be good. These are individuals and usually have had no presenting symptoms before. At least, anything that has come to anyone's attention. So, it can't develop a model just based on symptomatic presentation and a quicker analysis after that.

Next slide, please.

With population screening outside the newborn period, would it feasible or desirable. And they concluded, yes, that would be true if diagnosis was predictable with severity. That's the problem. We can't really understand it, it's a very level of understanding. Just because you have a genetic abnormality, for example, we don't know whether you have the disease or not. So, telling people you might die, or telling people may need to go on some kind of regimen, is a serious thing to be telling people. Next slide.

The absence of population screening, what would be the best case scenario for early identification? We could have a more systematic screening for some of the symptoms that do occur in anticipation of an event and/or assessing family history. There could be a more systematic inclusion of some of these guidelines into pediatric or adolescent care. Again, it's not going to identify asymptomatic. Next slide.

Beth -- you skip a slide – so, Beth concluded that to truly change the current paradigm would be heroic because of the combination of challenges associated with both the diagnosis and uncertain future presentation. Next slide.

There are a variety of different stakeholder groups that would need to be engaged if we had any discussions about altering current practice. Cardiologist, genetics, primary care physicians, patients and families. Next slide.

Again, we will be continuing this discussion. We'll have a discussion about Wilson's disease next meeting. Their original plan was to maybe have a preliminary report to you at the end of that meeting, but that's not going to happen. We will hear what we hear about Wilson's disease and then we will ponder all this and work on it in the interim period before May. Beth, I represent you and your slides on that. Did I miss state anything? [Laughter]

All right. I think that is the last slide. I think this is going to be a challenge for us. We don't really know what we are going to end up recommending to this committee. Ultimately, from the committee's perspective, right now, we are recommending things to the Secretary for the RUSP. Somehow, I don't think this would be the pathway for these kinds of diseases or conditions. It would probably be ultimately a practice guideline that would be recommending things that would happen. Now, if we ended up saying we think population screening for fragile X ought to happen at age two or for long QT or Wilson's disease, I'm sure Pierre will have some thoughts about that. But, for us, this is a useful activity, still. The committee -- I think we are responsible for thinking about these more broadly. But, whether there is – a clear thing we could send to Alex and do a condition review to tell us what to do with this disease. You ready for the hand of? Okay, great. Well, that's a good sign. It will be a different process. I think I will stop talking and open it up for questions.

Okay. Thank you, Don. Let's open this for discussion, questions first from the committee.

This is Coleen. A wonderful presentation. Just in respect to the last item, maybe thinking about childhood onset conditions and ones that maybe aren't appropriate yet for newborn screening. Going back to the discussion yesterday with carrier testing. I know you are not there yet. Maybe this is the light at the end of the tunnel. Thinking about how the committee could provide guidance through a workgroup, in terms of issues to think about. Sometimes, some of the ethical, legal, or social issues and considering these conditions. The same type of thing -- the place we went back to yesterday, in terms of carrier testing, thinking about that as a commonality across these conditions.

Sure. Beth, -- [Indiscernible-low volume]

I was on a working group that HRSA started. I first thought we should go back to what, Dr. Copeland commissioned the group on carrier screening. I think it's a good point that we want to go back where we left off. I'm not sure. I think it might have even been presented -- the summary document -- in spring. So, that's one place we can pick up from where we left off.

This is Charlie Homer from the committee. I may have missed this comment. One of my questions -- they might be addressed within those. If it meets the criteria for screening, the committee, why couldn't it be done in the newborn period, rather than later? Again, that's where we have captured and will be the test, like an EKG. As long as you are doing and an echo, a pulse ox, -- obviously, if I look at all of these, I'm just wondering if they meet the criteria for screening, why not do it? But, I'm probably missing something.

It's a great question and we certainly have that question in fragile X and my own research has been on newborn screening for fragile X for a number of years now. Watching the reviews that Alex produces, it would not meet the standard right now. There's no treatment in the way that we are considering treatment outcome, in terms of clear evidence in identifying a baby with fragile X would dramatically change – that we had a treatment that would dramatically change the treatment or trajectory for that child. I would argue in terms of the committee's decisions, it's not really for prime time now. All of these, they are rapidly changing landscapes. There are clinical trials ongoing right now in children age 5 and older for medications for fragile X that are more disease specific, that could change the dynamic very quickly for all these adults. The thing we've tried to say is, if it doesn't meet the criteria right now, would still be beneficial to identify it earlier than we are identifying right now? We may end up concluding that it's just too difficult a task for us. I'm not invested in that, yet.

This is Alex Kemper. One thing I wanted to clarify, I guess just ambiguate the evidence review process from the decision process. Our evidence review process, when changed, is just a matter for you all who would be voting on it, whether or not you think the benefit accrues in early childhood versus later childhood, whether or not there's a rationale for doing newborn screening versus older screening. The evidence review process itself wouldn't change. Some of the key questions might be targeted a little bit differently. Again, this afternoon, we have an analytic framework that would allow that to happen.

Chris, I think you asked the same question at our last meeting about fragile X, why not just go ahead with newborn screening for it? Do you have --

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[Indiscernible-low volume]

This is actually a little bit different. I guess, at the end of it, you said what about a clinical recommendation, a clinical guideline? There is a group that deals with that. I think this really gets into the discussion about population-based screening, getting everybody. To me, there are some reason if we are talking about everybody having health insurance, the healthcare delivery system is a way of looking at it. The thing to think about and the group should look at, there are already things to do screening for that have some hereditary. Autism screening stands out as one of them. When you do it clinically, which we measure in their performance measures, you never get to 100% or even close to that amount of people screening. I think there is a big discussion about whether we are talking about population-based screening involving public health to try to get that involved, or whether it is the purview of how we relate to current home

practice recommendations, like bright futures, that includes things that are listed as population-based screening within a practice.

This is Andrea Williams. I think it's important not to relax the standards as we move forward, so the test specificity and sensitivity is not lost, so in this later part, we are going to do a little less or require a little less than that. This is Kathy Wicklund. The other thing to consider is what's happening in the prenatal world of fragile X and certainly, a lot of centers are automatically offering fragile X carrier testing to all pregnant women as well. How that can impact this is also a factor to consider.

Certainly that is happening. We're the committee on newborns and children, that's what we are for pursuing our efforts on right now. Clearly, that's going to happen for everything we are studying.

Additional questions or comments? There is a question from the public for Don from, it looks like Mei Baker. Does the committee have an interest in birth hospital regarding newborn screening?

If I understand your question, in terms of the broader mission as our subcommittee on not really the specific topic. What would be other kinds of information that would be provided in the birthing hospital regarding newborn screening? Certainly, that is within the purview of this committee. I don't know if the topic has anything to say about that, in terms of what Genetic Alliance is doing with birth education. Also, I know that we have a number of other subcommittee members that are -- I guess it wasn't a short answer. The long answer is, we are not doing anything on that right now, but we hear what you are saying.

This is Natasha, can you guys hear me? In terms of what we have been doing, Baby's First Test, around birthing hospital education, we have distributed a number of different materials and we have worked with a number of nurse midwives doing some training. We actually did a training here in D.C. in the local birthing centers. So, we're really trying to reach different people who would be involved in a woman's pregnancy and delivery. It is something that we continue -- want to work with people on and be able to target those birthing hospitals, because that's really where the newborn screening may be taking place and to really be able to get the education into places where people would most likely be taking it out. That would be the time when newborn screening is happening, or maybe before then. We are interested in being able to partner with other people who have projects. A lot of our child centers to focus on birthing hospitals. That may be another opportunity to support those programs throughout the country.

Thank you, Natasha. That certainly is something that the subcommittee can consider, to help, kind of, make this into a potential project in the future, as a focus to round out some of the educational activities you spoke about.

Cate?

This is Cate Walsh Vockley. Just to highlight some other educational activities, I work with the Babies Through Screening Foundation. We do pretty aggressively market our videos and educational materials through professional meetings like the Association of Nurse Midwives, try to reach out to people who are involved in perinatal care, so that the education is happening prior to delivery.

Thanks everyone for this input. Another quick comment and Beth will that that say something. I think your comment about practice guidelines is an important one. We also have to ask, is that really the job of this committee? To deal with practice guidelines, or do other groups do that? My guess is that other groups do that and it's not within our purview. However, we might be making some more general statements about the importance of earlier identification of conditions and think across diseases about what might be screening guidelines and practices. It could be applicable to a number of different -- I don't know if that's possible or not. I don't believe that's our job of getting practice guidelines for every disease. Beth, you want to say anything?

To go back to the earlier comment, Dr. Homer, about newborn screening, I think the problem with Long QT is different from the fragile X problem in that I think you don't have the test is not right up to par yet with predictability. It's only seemingly available in abstract. They are only able to find mutations in 50% of the children whose EKGs come up as positive. And so you are left with 50% of children with EKG finding but no genetic finding, so you are not sure whether or not those children have Long QT. Conversely, Long QT can be variable and you don't find in the prenatal period, it could come up later, conceivably. I'm not a cardiologist. My understanding is it's a variable presentation on the ECG. So, a negative genetic test does not mean you don't have long QT. This condition is particularly problematic for newborn screening because of the screening and diagnostic algorithms that currently exist.

Jeff Botkin. I'm not sure at this point whether this committee has the right makeup or authority to address screening with older kids. It's part of our title. I'm not sure we have the membership or respect from the other communities to do that. But, I do think the methodologies have been developed through the committee and would be very helpful to other groups. We ought to be making sure that the methods that are developed here are published. My guess is that could be a real contribution to other groups who may have more direct authority over screening of different types.

Thanks Jeff. That's a great comment. Our meeting yesterday wasn't boring and we had some great discussions and look forward to continue to work on these activities.

Thank you, Don, very much. Thank everybody for your contributions to the discussion. Next, we have her report from the Subcommittee on Follow-up and Treatment.

Carol, will you be making the presentation?

We also had a lively and interesting meeting. Presenting on behalf of a wonderful subcommittee and co-chair Chris, who will be presenting part of our report today. Next slide. This is just to show that we are active. There are members of the subcommittee and in preparing the slide, Jill, who is highlighted, is also on the committee itself or a liaison. There are liaisons from HRSA and people who have been asked to contribute to specific expertise. Next slide.

This is to remind you going back to 2011, the charge of the subcommittee is to — multi-steps sometimes means one of our projects might build off of the previous project — identify barriers to implementation of short and long-term follow-up and that, obviously, includes treatment for people with conditions discovered by newborn screening. To develop recommendations to overcoming identified barriers, to improve implementation and to offer guidance on responsibility for implementation for long-term follow-up. Next slide.

So, what we have done since the meeting last May, we continue to have monthly phone calls. We are working on the priority areas and projects that were previously assigned by the committee. I'm going to report on -- actually, Chris is going to report on priority A. Roger. I'm going to report on the status of priority C project. We continued working on those projects. Before I get there in the next slide, to remind the committee that we have -- that was A and C. That we have priority D. We do not have a specific project at this moment assigned to us. From priority B, we were asked to consider the roles and responsibilities of the various players and long-term follow-up, but no specific projects. It was agreed that we would, and all of our case studies, or any other projects we would include focus on learning what are the current and highly variable roles and responsibilities for long-term follow-up. Those were projects -- the prior A project focused on implementation of hearing screening and the priority C project focused on understanding about comes, using sickle cell as an example. We were asked by the committee to make sure that all our projects look at roles and responsibilities. I'm not saying what they should be, but examining what they are. Next slide — Chris

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Yes. This one is entitled “Lessons Learned from Early Hearing Detection and Intervention that may be applicable to Critical Congenital Heart Disease Screening. You have a copy of the latest draft of this paper. At the previous meeting, I had put out the major points that we were talking about. This paper fleshes out some of the content behind that in terms of lessons learned. I'm going to highlight some changes that we've made. We've had some discussion yesterday at our meeting to make some other changes. I really want to get a committee input on -- are we going in the right direction? Does this seem to be helpful? I think we are thinking that this is more of a commentary that could be published as an editorial piece in one of the journals. So, with that, that's kind of where we are looking at it. To give you some highlights, as opposed to lessons learned, I put some lessons, we are definitely not saying this is all the lessons learned. We had some discussions that the paper really is heavy on data integration and maybe not as much in terms of program. That's the discussion we've had. The other thing, -- next slide --

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This is what I'm going to get into. It's teamwork. We actually had a lot of people call in yesterday, too. I don't know if we had as many, it was pretty high, I think it was in the 20s. There is interest in this committee. [Laughter]

No competition. Unless we did have more. [Laughter]

Okay. The other point -- even though this talks about the Early Hearing Detection and Intervention (EHDI) project, but ideas that some of the things that come out of this paper would be lessons that could be applicable to other point of care screening. That's put in the background statement. As far as the lessons learned, the first one really talks about the integration of screening. In particular, the challenges that happen when you talk about point of care screening and what's learned from the EHDI and newborn blood spot screening program that, in various places, they are not as well integrated. Coleen brought up the idea of, what's the importance of that? The importance really is moving toward the idea of projects that talk about child health integration and the idea of having one place we can look at the results of everything. I also think that when you talk about -- talking about your newborn screening program, there are some advantages in saying our newborn screening program includes blood spot screening, hearing screening, CCHD screening, there's economies of scale when you put out information about that. That's one of the first points. The second point is the one where we have a lot more examples of discussion, which is that the state health departments should play a leadership role in implementing electronic data systems that utilize standards-based messaging to reduce errors in enhance timeliness and data reporting. This comes from the idea with the program -- the EHDI program – that you can have the screen and electronically communicate the results. There something similar with regard to CCHD and integrating that aspect. The material that's in the document really talks about where states are, what are some good examples, we are working on that.

The third one talks about screening programs should require child-level data for quality improvement efforts. We got into some of that discussion yesterday, the idea that we are talking about clinical care and also talking about public health monitoring. Without the individual data, it's hard to say that you've screened everybody. It's also hard to be able to say this is somebody that needs to be screened or that were missed, that could have some effect in terms of clinical care. The last point, which I think I'm going to change to say appropriate support, federal and state, will be needed to develop, implement, and maintain the CCHD screening system. It's not just money, it's also technical assistance. HRSA put out grants for states to do this. It's the kind of this report you need as you add other point of care screenings or other screenings to the systems. I'm going to stop here and see if people have comments. Certainly, on your home, you can read the document and send us your information. We are going to meet -- make a few changes. One of the things is there are references that will make the background in terms of publishing it. The other thing, when we think about what committees can do, is that when you look at this, we want to get it out to folks. They're developing the programs. That's one of the things the committee can help with. It's also interesting that we have state that have a grant to develop CCHD screening and it would be

interesting to learn -- are they working and some of these -- are they learning some of these lessons or doing them? I will stop here.

Let's open this up for questions and comments. Okay. Now, we can open this for questions and/or comments from committee, first. Coleen?

Thank you very much, Chris and colleagues, who developed the white paper. I did read it last night. So, I apologize for my delay in reading it, other than the high-level summary from yesterday. I thought it had some really, really good points. I'm wondering if they are going to get lost, because you are focusing on services -- lessons learned from EHDI that are appropriate for new point-of-care issues. I thought all three of those, the first three, the integrated child test idea, the importance of electronic health exchange and this is the case for whether it's -- essentially, a public health function integrating with the clinical function. That's essential to work well. They have to come on board with that. The last thing was with the need for individual level data, essential for quality improvement issues. I wonder if you guys should go forward with this, maybe generalize it a bit more. Don't just have that narrow form of EHDI versus -- these are critical issues on long-term follow-up and tracking data, maybe expanding that second piece a bit more. I thought you did a wonderful job with the examples that were in there. They were right on point, maybe expanding the second one. The third one -- what are we missing by not having that individual level data. It's very brief in there, but actually has some examples for the future. Thanks.

Just a response. I look forward to your specific comments that you can send about wording and everything like that. I think that's an important point. At the same thing -- the same thing, when you start doing this over and over again, there is that major point that being a state that started EHDI where it didn't do individual data, despite my recommendation that we do. But, that really does set you up for issues down the road, in terms of what people expect and that kind of stuff. If you are really talking about doing, which I think we are saying, that it is the idea that we are monitoring and we want to get quality care. You've got to have that information. I will go through that and try to do that.

Okay. Great. Additional questions or comments?

I think this draft is in process. So, it doesn't really need to come in final form to the committee at the present time period as you develop it, if it's completed prior to the next meeting, I think the committee could then accept it and we can go forward. Like the comments that were made, I think Coleen's comments are right on target. I think broadening it to include these issues related to newborn screening in general. I know the initial thing was this point of care was happening. It's very clear that it represents making that more effective. I think that's really good. Before we get to the rest of the report, I just want to remind the public, those on the webinar, that you can ask a question. If you go and type it in on the lower left-hand corner -- in the middle – okay –you can send it to us. We will attempt to answer that, as well, in the course of discussion. Carol, back to you.

Okay. If we go back one slide, thank you. Originally, the committee had envisioned a possible follow-up project to focus on implementation of CCHD. When we get to the part where we talk about, as Dr Bocchini asked us to – what the subcommittee might be asked by the committee to do going forward, we are going to suggest that we don't think this is such a great idea at this point. There are HRSA projects specifically looking at this. One of the possible follow-up projects to this point of care, of some lessons learned, could, for example, be to develop -- explore what's going on and report on best practices and how people are handling the data management after point of care screening. But, that's one possibility. . We want to be very specific. We were tasked to think about doing a follow-up project and there was a consensus that we think that's a bad idea. Going forward, next slide -- and one more -- two slides forward, please.

So, our priority C project, framework for assessing outcomes for newborn screening, do we know if we are achieving the promise of newborn screening? I am showing the same slides before, just to review the history. Very emphatically and explicitly, we are not duplicating other efforts at HHS. We have lots of people with expertise in sickle cell, which is our example on the subcommittee and participating as part of the workgroup. I don't know if workgroup -- maybe that's too formal a word, as our ad hoc writing group work so, the idea is to focus on developing key questions, understanding what are the data sources, identifying gaps and working on creating a framework. The idea is to use sickle cell as an example as we are developing that framework, and test it against sickle cell. We now have some more specific ideas about how we will test it against other disorders. The idea is to develop a framework that can be applied to any disorder. Next slide.

Where we stand now, is that we have a draft. Actually, we are two drafts beyond what the committee has because we are continuing to do some work. The newest draft is markedly improved, but you haven't seen it yet, because Charlie Homer, who has a lot of expertise and quality improvements, has done a major, major edit. We have a draft that we have given to the committee. The focus is on harmonization of, avoidance of duplication. How can we help people to know what kind of data ought to be collected? That relates back to what kind of long-term follow-up is necessary. The goal is to find out what management people are receiving and what are the outcomes, so you can actually go back and answer, not only questions of newborn screening to reach better outcome, but what in the process -- what about the activities and actions after the newborn screening are making a difference? What's being missed, what's being done? Is this something being done that doesn't lead to better outcomes? Is something being missed at we know should lead to better outcomes?

It is a work in progress and we are at a point where we would really like to get feedback from the committee. So, we want to give a couple of minutes -- I have only five minutes for the rest of the whole committee report. So, we will want to get feedback from the committee to get a sense if we are on the right track. One of the things that we did give you last time, but not this time, is a version of the framework of the table that is blank. But, as you are thinking about it, remember, this is not about doing the project. This is not about selecting the data. This is about what kinds of data ought to be collected, using sickle cell as an example. I can tell you, we just

created a small work group that will actually consider what would happen if we tried to put PK2 or one of the inborn errors of metabolism in there to see -- does the framework work for another disorder? Does looking at another disorder show us that somebody used blank spots that we simply haven't realized? Because there needs to be a place or something? The suggestion was made, PKU is a condition where we have many, many years of experience but not much in the way of formal data collection. Some of the data collection is being led by HRSA support to Mary, she will be part of that group. We are making sure we focus on harmonization and building what resources are there. Another point made is there's another group which has lots and lots and lots of data. That is to figure out how to approach the CF community and see whether that framework would work for them. To do that, I think we would need to -- we don't have anybody in the SCID committee, currently, on our subcommittee. So, we want to be very mindful of not showing ongoing work of the subcommittee, outside of the subcommittee. But, we would like to share the framework with the CF community. The next thing before I have my last couple of slides, and thinking about the brainstorming, is to ask for feedback from the committee on the draft that we had provided, recognizing it's already in the process of changing. Before we change it too much, are we on the right track? Last I we were told we were on the right track, it moved forward. We want to make sure we are still on the right track.

So, let's open this portion of the report to discussion. Any questions or comments? Concerning this priority C?

If not, my feeling is that you are on track. I think that the additional discussions you have, it certainly involves the project, to where, it will have broader opportunity, to build the framework that I think we're looking for, in order to evaluate long-term follow-up. I think that we are going in the right direction.

Thank you. I also probably should say, now, so it's part of the subcommittee report, that yesterday, we felt very strongly -- after Beth Tarini's presentation -- that we are on the right track. You're pulling together all kinds of questions that will help people address some of the lack of harmonization that was coming across in her study. Probably, also useful to look ahead -- I don't have a slide for this -- on the agenda for the subcommittee, we did hear a report from Debbie Badawi in Maryland. She reported on the just about to start project she has, a HRSA study called Coordination Outcomes and Information and Long-term Newborn Screening Follow-up. We understand that's one of two grants that was awarded. The other is in California. It's California, Hawaii, and other parts of the West Coast. These are projects to explore some of the implementation aspect of information, and I think I'm getting a little off-track. The integration of newborn screening, long-term follow-up, and the primary care, is the focus of the project.

As it happens, Maryland will be looking at sickle cell. They're just in the process of starting up, and have agreed. She has agreed it would be useful to use the framework, to see if it would help her to determine what kind of questions they should be following up. We are actually, in a sense, going to have another pilot of the framework and we also would very much like to hear,

at a future meeting, of the subcommittee -- possibly in our next telephone meeting -- from the West Coast project, to hear what's going on there.

The last thing in new business -- of notification -- and then, very briefly, the new business with the brainstorming.

We were informed. I think Coleen is the one who told us -- that the FDA had made her aware that they will either shortly or have just published for public comment, a new guidance on medical foods. They wanted our subcommittee to be aware of that.

The last slide is blank. It's just new business. So, [Laughter] -- yeah, we are — we have some ideas.

We are moving forward, looking forward to the future, to complete the white paper on some lessons learned from EHDI. We think the next time we will be back for approval from the committee with the changes, as Jeff suggested, and possible that we would have some -- if the committee would like -- that there could be some follow-up to that. We definitely are on track to complete the framework and it was suggested by Charlie Homer and if people are using it, that there might be potential value of convening a meeting of the appropriate stakeholders for the utilization of that. So, a possible follow-up project there. We continue to be, as you know from the minutes of last meeting were approved, the subcommittee continues to be interested in ways that the subcommittee could be useful to help the committee frame questions convened in reports on discussion among appropriate partners, that leads to understanding of any gaps or obstacles to services for children with hereditary diseases. The ultimate goal is promoting access to quality care. We floated some ideas. As other subcommittees mentioned, challenging questions or projects that are neither too broad, to be actually carried out, or too narrow to be appropriate as a subcommittee project. If it's narrow enough, somebody could get it funded with a specific project. It's really a role of the subcommittee to help the committee to convene conversation across disciplines and stakeholders. So, we are open to suggestions. We do have some examples is access to care. One example is how we could envision and implement team healthcare. This is brainstorming as we walked back to the subway, building off some ideas in the subcommittee discussion. Team healthcare for children with heritable disorders going forward, an approach could be to convene appropriate shareholders to explore what we can learn from other people providing care for non-heritable disorders that could apply to heritable disorders and what may be unique challenges for the heritable disorders, including time, resources such as workforce. Another example would be to the delivery system for heritable disorders and an example of this from Charlie Homer, is accountable care organizations and capitation, and how that interacts with the medical home and the specialist's and the of children with heritable disorders. Chris points out this may be premature. There aren't very many mature accountable care organizations. On the other hand, that could make it a really appropriate time to do something, as they are beginning to develop their systems. How would our particular population of vulnerable infants and families be better served? Some ideas, but nothing -- like the first committee report -- nothing so definite that we have a specific

project to put forward. But, some ideas of interest and we look forward to guidance. The, we still have plenty of work to do with what we've got.

Thank you very much. Any additional questions, comments? From the committee or liaisons?

I think those are good suggestions for us to consider. I think that I'd like the committee members to think about these things and -- what's going to happen, as you know from what I mentioned yesterday, we are going to summarize this meeting and send the Secretary a summary of what not only the committee is doing, but the projects that some of the subcommittees have undertaken and the progress of those. In addition, we ought to be thinking about how to proceed with some of those suggestions and try to make them into specific projects, over time period but --

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If there are no additional questions or comments, let's go to the public comment.

We have three individuals who wish to make oral comments. Each individual will be limited to five minutes of speaking time period. So, the three individuals are -- they should be queued in this sequence. So, this is a reminder. The individuals making oral comments, please be sure that you have your computer speakers turned off. Before speaking, please state your name and organization. Operator, would you please open the line for Sarah Wilkerson, a board member of Save Babies through Screening Foundation.

Your line is open.

Can everybody hear me okay?

Yes, we can hear you.

Thank you, I am Sarah Wilkerson. I'm here to speak to today as a mother and a member of the board for the Save Babies through Screening Foundation. My son Noah died at a few days old from undiagnosed MCAT. His diagnosis came a day after his death, too late for my husband and I to be able to do anything to save him. Upon further investigation, we learned about a number of delays that are allowed for in the current system and many states across the country, and I urge you do consider creating clear guidelines for how test samples should be handled so that babies like Noah don't slip through the cracks. These guidelines would include limit the window time hospitals have to take the initial board sample to 24 to 48 hours of life. No longer allow the use of the U.S. Postal Service to send in samples. A courier service should be used. As many as 16 states still allow for snail mail, and this adds a couple of unnecessary days to the process right there. Prohibit batching, which still happens in the more rural areas of the country where less is known about newborn screening, better education in these areas is sorely needed, and encourage labs to use their funding to keep the labs open on Saturdays, or at least vary the shifts in the lab so that it's continuously staffed. Twenty six states are completely closed on weekends, and babies are born every day of the week, regardless of weekends or holidays. There’s time and emphasis from the committee spent on treatment options, education, and so

forth, but with turnaround time on newborn screening test results it's so important to consider this as well. Without proper identification of these illnesses in a timely fashion, all of the follow-up steps don't matter. My husband and I would've given anything to have had the opportunity to care for our son, the way he deserved to, with a very well established treatment plan for MCAT children. It's essential for you to understand this as well, and are willing to empower parents with information they deserve to have about their children in a timely fashion. Thank you for your consideration.

Ms. Wilkerson, thank you for your comments. We appreciate them and, certainly, these are things for consideration by the committee.

Thank you.

Will you open the phone line for Dr. Amber Salzman, who is president of the Stop ALD Foundation?

Your line is open.

This is Dr. Amber Salzman. I am with the Stop ALD Foundation. The purpose of my comments today is to provide a further update on newborn screening for Adrenoleukodystrophy (ALD) with the aspiration of moving the review process forward. At the September 2012 Secretaries Advisory Committee Meeting, the ALD newborn screening nomination was reviewed. The Committee recognized ALD, and I quote, “as a medically important disorder that deserves serious consideration, possessing a well-established case definition as well as screening, diagnostic, and treatment protocols” end quote. However, the committee requested more prospective data from the Mayo Biochemical Genetics Laboratory (MBGL). They had a pilot that was moving forward. Once additional data became available, we were encouraged to contact the committee to facilitate an expedited review. The committee would then determine whether the data merits a formal review of the scientific evidence by the external condition review workgroup. With that as a context, I provided an update on the MBGL pilot at the last committee meeting in April, and sent in an update to the Committee last month. I'd further appreciate the opportunity to review the status of the pilot today. Okay. So far, 75,000 samples have been screened and analyzed. As to the two-tier approach, 10 samples were submitted from molecular testing. Of those 10 samples, four samples were found to be positive for a mutation in the ABCD1 gene, which is the gene responsible for ALD. So, in summary, there is a reliable approach to doing a biochemical screen of blood spots. Mechanisms are in place to do molecular screening on the samples that become positive by biochemical screening. It's been published in several studies and reinforced by experts in the field that early warning is the only way to assure children are treated in time for therapy to be effective. We do not want any more families to unnecessarily suffer the devastation ALD can cause when it's diagnosed too late to intervene. Given the recommendation from the September 2012 review of ALD and the updated data from the Mayo pilot that was submitted a month ago, we hope you can provide guidance on how to best work with the Committee to move forward expeditiously to review ALD and address any concerns that may exist. Thank you so very much for your time.

Thank you for your comments, Dr. Salzman. We do have the data and the plan is to move that forward to the Nomination and Prioritization Committee, subcommittee, so that it can be reviewed for decisions at the next meeting on whether to move the nominated condition onto evidence review. Thank you.

The next individual is Dr. Kenneth Pass. Operator, if you will please open the phone lines for Kenneth Pass. He is the former director of the New York State Newborn Screening Program. Dr.Pass?

Operator, -- I do not have that connection. Are you sitting with someone else, perhaps?

No. Actually, that was listed as not confirmed. But there was an original request for him to make public comments. So, if he's not on the line, then that will conclude the public comment section for all the individuals who had indicated they wished to make comments. So, with that, we have finished this morning's agenda. So, --

Dr. Matern?

I just have a question with respect to the public comments that were in our package. There was one that I found disturbing, which may have been disturbed. I just wonder, do we file it away or do we respond to that?

Debi, do you want to address --

Do you have a specific comment that you are raising?

The comment was from a Jean public and it was to this committee and to speaker [Indiscernible], etcetera.

So, the public comments are written and are part of the record. I had not set aside time on the agenda to respond to every public comment. So, right now, we do not need to respond. But if you would like to, we can segue into doing that. We can do it during lunch or after the meeting.

That public comment you are referring to, I believe it was from the May meeting, it wasn't submitted this time around.

That's possible.

It was related to the prior meeting.

Okay. Carol?

Carol Greene. This ties together the very succinct and eloquent comment, public comment, about the timing of newborn screening and handling of samples with something that I understand was raised -- for-point of information -- to this Lab Follow-up Committee, I don't think -- I don't think I heard it mentioned in the full committee. But, I understand that the APHL reported to the Lab Subcommittee that they are engaging in a project to look at the impact of the recently released MMWR with guidelines for biochemical genetics testing, and those guidelines for biochemical genetics testing did include some guidelines for those aspects of biochemical genetics testing that are done in newborn screening labs. One of the specific things that was included in those guidelines, I know because I was involved in the writing, of the original workgroup report, was the danger of relying on the mail, the importance of timely delivery of samples to the system. So, that does tie together something that I believe the APHL had wanted to make known to the -- it's CCHD and APHL project. I know the CCHD wanted to make known to this committee that this project is going forward. The CCHD had previously noted but -- notified this Committee when the MMWR was published. That may be an opportunity to explore with laboratories, how they are using the guidelines and whether those guidelines are helping them to address some of the concerns about timely delivery of samples.

Alright. Thank you for that comment. Colleen?

Thank you very much. So, I guess I've heard -- I don't know much about the front end of newborn screening, the laboratory and how it operates within the context of the public health department. I've been working on sort of the back end. But, I guess I'm listening to Ms. Wilkerson, and her challenges to us, about some of the remaining complexities of a system that is very dispersed. I'm just wondering -- are these issues that we are dealing with this in the context of the laboratory subcommittee? Is this an issue we need to bring to the larger committee? These seem like issues that we could address and we could solve. I just wonder -- I want to get others opinions of that.

I think that's an excellent comment. Clearly, as I stated, I believe this is under the purview of the committee. So, I think if there are additional comments, I would certainly like to hear them. I think this is something that, especially with Carol's comment about CDC and APHL being interested in addressing some of this as part of the review, it would be nice to find out what's being done and what's happening. And, whether this is time to address potential changes to improve timeliness of submission of specimens. I agree. So, if the committee is an agreement, we will move this as a request to the Laboratory Committee, to look into this issue and see what's being done and see what's available and see if there can be something that can come as a recommendation from this committee going forward.

And also schedule a time at the January meeting for CDC and APHL to present, as well. They can work with the Lab committee.

Agreed. Everybody is in agreement? Okay. Great. Okay. Any additional things to come forward?

All right. If not, we are going to take a break for lunch now. We'd like everybody back here promptly at 1:00 p.m. Thank you all very much.

[The DACHDNC Webinar is on break for lunch, and will resume at 1:00 pm Eastern Time].

Afternoon Session

Good Afternoon. Welcome to the second session, of the second day of our meeting. Before we begin to get into the presentations, we need to conduct an additional roll call. So, we'll go committee roll call first. Don Bailey?

Here.

I'm here. Jeff Botkin?

Here.

Coleen Boyle?

Here.

Denise Dougherty?

Here.

Charlie Homer? Still coming back. Kellie Kelm?

Here.

Fred Lorey? Ok. Michael Lu?

Here.

Steve McDonough?

Here.

Dieter Matern?

Here.

Melissa Parisi?

Here.

Alexis Thompson is absent.

Cathy Wicklund?

Here.

Andrea Williams?

Here.

Debbie Sarkar.

Here.

Now for the organizational representatives expected to be in attendance. So Beth Tarini?

Here.

Michael Watson is unable because he's on a plane. Mindy Saraco?

Here.

Thank you. Kate Taft or Carolyn Mullen? Okay, Susan Tanksley?

Here.

Chris Kus?

Here.

Adam Kanis?

Here.

Natasha Bonhomme?

Here.

Cate Vockley?

Here.

And, Carol Greene?

Here.

Okay, that will complete the attendance so we're going to change the presentation schedule this afternoon and have our second speaker go first. We'll hear an update on the MPS 1 evidence review by Alex Kemper, and Dr. Kemper is a general pediatrician and Director of the program on health services research at Duke University. His research focuses on the implementation and evaluation of screening programs for children, including newborn screening, screening for visual impairment and screening for lead poisoning. Dr. Kemper is also Associate Editor for Pediatrics, the official journal of the American Academy of Pediatrics. So Alex, I'll turn it over to you.

So, good afternoon everyone. I appreciate this opportunity to update you with where our group is and also to take this opportunity to ask you all for advice about directions that we can take. Can I have the next slide please?

So first of course I'd like to thank everyone who's a member of the Condition Review Work group. Our members work really hard, and I'm fortunate to be able to work with such knowledgeable and energetic people.

So really what I'd like to do is talk about two things. One is a revised version of the conceptual framework that we used when we assessed newborn screening, based on lessons that we've learned from all of the previous reviews that we've done, including our experience from looking at Pompe Disease, and the public health impact assessment that was related to that as was brought up this morning, I think that this is, like, a fine time to really take a step back and look at how we do things and think about how we can make the process even better, and then the second thing I'd like to do is provide an update with where we are with the MPS1 condition review, including talking about the technical expert panel that we've had and where we are in the evidence review process and again, I'd like specific advice about where we can take things as we do this review. Next slide please.

So let's first talk about the conceptual model. So this is the model that we've used really in all the previous reviews that we've done. This is a model that's been well vetted, it's used by the U.S. Preventive Services Task Force and the community guide and it's really, just use the model by many, but the problem was that there are many additional questions that we look at as we do these newborn screening reviews, that this model really doesn't lend itself to addressing, including the public health impact. So we really thought that now is the time to take a step back and rethink this. Now, before I bring up the model, the one thing that I would remind you is that this is just a model. It's not reality. It's a simplification of reality. It doesn't show things like timelines and lots of nuance but it's something that we use to make sure that as we do the evidence review, and by that I mean all three components, the systematic evidence review, the modeling component ,and the public health impact assessment, that we really consider everything and again, our goal in making sure that we think through all of these questions is we

want to make sure that we can inform the advisory committee as best we can to help facilitate the complex issue of decision-making. So with that kind of caveat, next slide please.

These again were the old key questions. I'm not going to read them to the group again, but I just want to just point out that these questions are tied to that analytic framework but one of the challenges that we face is that these key questions are really at the 30,000-foot level, and I want to make sure that we're thinking through the nuance of the conditions so that when we present the reviews, we're hitting everything. Okay, so now the next slide.

Maybe it's one more after this, so okay I apologize. There we go, perfect! This is the brand new conceptual framework and the only thing that upsets me, of course now, that I look at it is it has a lot of Carolina blue.

[LAUGHTER]

But we'll get through somehow.

[LAUGHTER]

So the issue, the conceptual framework, is first of all if you look at it far away divided into two halves. There's the half on the left that has to do with the process and screening and diagnosis, and the session on the right. So when you consider newborn screening, of course, you have that it begins with newborn screening, and then as newborn screening you can either have a positive or a negative screen, and if you have a negative screen it's almost like you're going into the process of usual care and that would be the case, for example, of the baby that had a false negative would be detected through the usual care system, but again we're comparing newborn screening to usual care. With usual care, there's a period of time when you're undiagnosed, and then for whatever reason you'll eventually come to diagnosis or not, and if you do get the diagnosis it will be confirmed and you'll enter into some treatment plan and that will be associated with outcomes. With newborn screening, you'll go through the period of diagnosis and confirmation. Through the diagnosis process, again, you'll either be confirmed to have whatever the targeted condition is or you might have an array of other things, including being unaffected, that is ,not having any condition, being a carrier or having some other condition being a secondary target, that kind of thing. In any case, then you enter into treatments and long term follow-up, and you can see where the usual care would also end up in having their health outcomes. That sort of ovoid shape is the outcomes. What I think just the different kind of outcomes that can happen, and we can debate around the words we use to describe these different measures. But I think, conceptually, is intermediate measures like, for example, biomarkers or some functional measure that's not necessarily a direct patient outcome. So, for a level of an analyte or maybe results from a pulmonary function test, as opposed to a primary health outcome, which would be something that would be more patient-centric, and then there's secondary outcome. So that’s kind of synthesized across the patient centric things, like maybe a more global sense of quality of life or impact of the family and so forth, and I'll show you examples of that later.

Now that thing on the left like a cylinder, that's where conceptually we're going to summarize the benefits and harms associated with screening and the short-term follow-up. And that cylinder on the right is where we synthesize across all of the stuff above it, in terms of the benefits and harms associated with treatments in long term follow-up. Now, all this stuff happens, all this Carolina blue stuff happens, within the context of the health system which again is related to, there's the public health system but also the healthcare service delivery system or the clinical care side of things. Again, there's different terms for these things, but what I think we had to be cognizant of is the various types of delivery of services that we have within the states. Now what we can see is there are numbers throughout this conceptual framework, and each of these things are linked to a series of questions. Some questions may be more appropriate for some conditions and less appropriate to others, so we're going to have to tweak things as we go along, but I want to show you exactly how this would play out.

So, each of those numbers, is now instead of just being a simple question, is what I call key topic questions or you can think of these as like broad areas. Again, these are terminologies our group came up with, but the main thing I want you to look at is just that we have these groupings. So we look at usual care, and the course associated with the condition, and look at issues related to screening and short-term follow-up, diagnosis and benefits and harms of the process of screening and diagnosis separate the treatments, treatment of long term follow-up, various outcomes that we spoke about, benefits and harms related to the treatment and long term follow up size things, and then healthcare system. But maybe a more better global term would be the health system, so that's the grouping of questions and now we'll drill further and talk about specific questions we plan to address. So, if I can have the next slide please.

So I apologize in advance. I know this seems like a long laundry list, but I think that it's important for us to think about these particular questions, and I would ask the advisory committee if they think of areas that we're not addressing, or maybe a different spin that we ought to put on these questions to let us know, and we have another evidence to discuss this. So as I go through these slides, if you notice that something's missing, please interrupt me. That didn't take very long did it?

[LAUGHTER]

Dr. Boyle?

So, on the model--

Can you go back a slide please?

I'm sorry. I thought it would be important to indicate, and it is on the U.S. services one that somehow you're identifying pre-symptomatic disease, and that is on the other one so that's apparent, so I know that it's inherent in this but it might be good to make it explicit?

That's perfect. So what we can do if you can go back to the previous slide please?

So in the newborn screening they have the short-term follow-up, they need to make it a little more explicit, maybe a little shading. Okay, so next slide, please and then one more after that?

Here we go, perfect.

So looking at the usual care side of things, and if you want to look at the framework as I go through that, I don't know if that's helpful or not, but what's the incidence of clinically detected MPS1? Again, because we're going to be looking at MPS1, I've dropped MPS1 into the terminology, so what's the incidence of clinically detected MPS1 in the United States? Of course it's critical for us to understand what's going on, now so that we can evaluate the benefit of screening. What's the distribution of MPS1 is in its various forms, and I'll be talking about the condition in a little bit. What's the incidence of pseudodeficiency and the average ages of symptom onset, diagnosis and treatment initiation for each of form of MPS1. So, the purpose of these questions is to give us a sense of what's going on through just typical clinical case detection. Everybody with me? For you in cyber space, there was a lot of nodding of the heads, which I hope to continue. Next slide, please?

So these are the, for key question two, these are the questions related to screening and short-term follow-up. So what are the analytic markers that are associated with MPS1 that can be used in population-based screening, what screening test can be used to find these markers? What's the analytic validity of the screening test for MPS1? If the markers present in dry blood spots will it be found? What's the clinical validity of available screening algorithm test in dry blood spots? Remember again that there's oftentimes algorithms in terms of repeat testing and that kind of thing, and if a screen test is positive how likely is it that the child has MPS1 that is what's the expected positive predicted volume in newborn screening. Are those most likely to benefit from early treatment identified by screening? Again, there's oftentimes a broad spectrum of the conditions which is put in there. Can screening, again before we move onto diagnosis, but at the time of screening can you predict the form of MPS1 carrier, status, or pseudodeficiency — has the screen test algorithm been evaluated to generate an understanding of the likely numbers and types of screening results? And is there a method of MPS1 screening quality assurance proficiency testing available for screening laboratories? So again, getting back to a comment that Dr. Lorey mentioned this morning, was about how the public health assessment is going to be incorporated into the report? One of the things that I wasn't clear, when I made my preamble comment, was that the report was like three columns, three separate things. There was the systematic review, the decision analytic modeling and the public health impact assessment, and one of the things that I really think that we can do better is make sure all three of those components are woven into one more common sense document, and that's why you'll see things before we might have considered to be more like, just pure public health impact assessment, for bringing up and looking at even earlier on. So there's those issues of Quality Assurance for the lab are obviously something that's very important. Dieter, do you a comment? Only positive ones.

[LAUGHTER]

Dieter Matern. Would you include a question about the long term availability of all of the reagents required for the test? There's at least one assay that looks at the immuno-glycogen that is under investigation, and as far as I know at least one of the reagents required is not all of the time available. So if you want to roll this out population wide it might be a limiting factor. One of the platforms that we are testing, the immunoassay, is probably not any commercial assay available long term at this point.

That's a good point and something that I hadn't considered, and you'll see that the gag test is one that's commonly used with an evaluation, so we will definitely add that in. Does anybody else have any comments about key questions before I talk about three? Seeing none, we'll move on.

So this is again related to key question or key topic question now. Diagnosis, what's the case definition, what approaches are available to diagnose MPS1 in newborns, what approaches are available to diagnose MPS1 in older children? The case of clinical detection as well, how are each of the forms of MPS1 identified, how is carrier status identified, how is pseudodeficiency identified, is the agreement on the diagnostic approaches, Quality Assurance programs available for proficiency testing of diagnostic laboratory? How long does it take to establish the diagnosis and how long does it take to rule out the diagnosis? And what other specific factors that may affect treatment plans or outcomes must be evaluated during the diagnostic period? So, an example just to clarify that, with Pompe Disease, there was a lot of talk around identifying the status during the process of diagnosis and I'm sure that it was, as we come out with other conditions, that we're looking at there were probably other things that need to be included in that diagnostic period. So that's a summary of the Question 3 group. Comments on this at all?

In the diagnostic phase, how do you consider other things that might be diagnosed, or is that something [inaudible] ?

Yeah, so that's definitely something and if you looked on the analytic framework and I probably just need to make it clear here too that there's all sorts of things like carriers, there's secondary conditions that could be identified or, who knows what. So my understanding with MPS1 and this is something we'll declare, probably the experts that come through. So if you're looking specifically at the enzyme deficiency associated specifically with MPS1, there aren't going to be other secondary conditions that would come up. But again, I could be wrong about that and if it does, you're exactly right, that needs to be made clear.

Okay, so this is the slide that has to do with the benefits of screening and diagnosis, separate from treatment, and before its always been hard especially to look at harms and we as a group decided that separating things up into the screening side and the diagnosis side that we would be better to look for the information but also be more clear when we explain it to the advisory committee. So what benefits to the child or the family are associated with pre-symptomatic

identification of MPS1, independent of the timing of treatment, so the one thing that you can already see, I stuck in to the benefits of the family, traditionally we only look at benefits to the child, and it may be beyond what the advisory committee wants us to look at. But since we are looking at the conceptual framework I wanted to raise that as issue, I expect that things might not come to a definitive conclusion on this but I think that it's something that we need to continue to talk about. The one thing, another thing that I forgot to say, if I got started, is that it's really important for us as a condition review work group to make sure that we're communicating with the advisory committee around these issues as well as just other granular things that might come up, and we're very fortunate to have Dr. Botkin and Dr. McDonough to be the liaisons to the advisory committee, so when we start wrestling with these things, certainly we'll be including the two of them in that conversation, and as a result the whole advisory committee. So, anyway, that's question one.

The next thing, to what extent does newborn screening change the observed incidence of spectrum of MPS1 compared to clinical detection? Everyone knows when you start screening, you find there's a much broader spectrum of the condition than you would have thought going into it. What physical and psychosocial harms are associated with other screening outcomes so false negatives, false positives, carrier status, pseudodeficiency. Does screening for MPS1 detect other conditions? Again, this goes back to what harms are associated with diagnosis, and diagnostic process of each form of MPS1, when detected through newborn screening? And again, that gets to, some conditions require much more intensive therapeutic maneuvers to come to diagnosis than others and then finally, what strategies out there can minimize the harms related to the screening and diagnostic process. So, do you want to talk about this or open it up for general questions about key topic four?

I think we can see if there's any question about four, and Don Bailey has a question for you.

Well, I just wanted to editorialize on the family question because I do think that it's important for us to consider. It might not be the ultimate determination, but I think that it's a piece of the equation. So when I was on the subcommittee that helped develop the scoring system that the ACMG used when they did the original scoring, and we were successful in adding family benefit into that scoring system and that did create some, I don't want to say pushback from the community, but we kept them in there, and so I think as a part of the review, certainly it should be something that should be in there.

Trying to understand how this model works, in terms of where the public health impact fits in, and if it all goes into that key topic Question 10, then certainly raise that then. But I thought I heard you say you were going to try to integrate through all of these questions, which kind of raises the question in terms of benefits and harms. There's benefits and harms to individuals but then there's also the benefits and harms, and mostly in terms of the cost to the healthcare system, as well to the public health programs. Do those go in here or would those all go into the black box?

Let me take that. So it's funny that I should have anticipated you were going to ask that question too. So, you know, it was hard figuring out logistically where to put the question. I mean the questions will come out and there's probably the same question could be repeated in multiple places, so I just made the arbitrary decision that when things could appear in multiple places like that I just kind of put them over there, and that's if you look at the conceptual framework where I have this kind of like little cylinders. That's where, because things were coming up so many times, oh, just those are the synthesis questions where things kind of go down. So I guess my reflection is that in the report, we hope to do a better job of being able to give one report that has all of these elements in it, and to make the report user friendly, we obviously can't have things repeated over so I was just going to kind of dump it into 10 or do people think that it would be helpful to change where things appear and I'm happy to do that, whatever you'd think makes more sense. Michael Lu, with HRSA, by the way. I want to make the comment, just in terms of the conceptual framework. It's really heavy, and really good on the systematic review and the analysis. It's still a little light on the public health side. Whether you look at the framework, it seems like a black box just kind of to help the public health system, in terms of the questions, whether it's an integrated issue or whether all of it goes into question number 10. Both questions are still under development. To do a really good job and have impact, we should give more thought about the conceptual framework.

This is Dr Kus. [Indiscernible]. Maybe I should ask you, Dr Bocchini. That's the part that makes me the most nervous. I think it's critical that you understand that before you make a recommendation. Some states are very sensitive about it and it's the one area that is more outside of my wheelhouse, so to speak, then the other parts. It would be great -- I kind of joked with Dr. Lorey about this this morning, right? If there could be somebody from the advisory committee who could help us go through that and give us advice.

Dr. Lorey has already agreed to do that. [Laughter]

I believe I was volunteered.

He was volunteered, but he did agree. So, he will be -- assist you and work with Jelili and you to trying and bring that along. I think that are first inclusion of that was in the last nomination that we did and approved, the nominated condition. I think this is a good time to strengthen that approach and strengthen the whole process.

Having Fred involved is a really good thing.

This is Alex Kemper. I really, really want to make sure that we get this as right as possible. I know we will get through the review and wish we had thought about this. It's going to continue to get better. Your help on this will be tremendous and there are some questions related to this.

It's Chris Kus. I think, related to Don's comment, it's the idea that when you say benefits and harms of screening and diagnosis, you put in the title “Benefits and Harms of Screening and

Diagnosis with Child and Family”? The other part could relate to the system. I would put in the idea that we are talking about the benefits of screening and diagnosis to child and family.

Yes. That's very good.

Carol Greene. I was heading for a similar comment. That is, recognizing the importance of addressing the impact on the public health system. One of the struggles that we have, when we are having conversations, is where we are looking at benefits and harms and putting in benefits and harms to the children versus the family. Family is not the role of the public health system versus the state versus the school. Who benefits? We need to get it all in there, but we need to put them out so we are not trying to come up with a single score of benefits that somehow puts together the public health system and the families. But, that when you get to the end, you see all those individual components, you can make decisions about how you want to weight them. We try to put public health in with the benefits to the child, that we are trying to compare things and it makes it a lot harder to have a conversation. It's very similar to what Chris just said, but perhaps with a little more detail and implementation.

This is Charlie Homer. I guess building on these comments, I think it is important -- I think it would be valuable for your work group, including Fred, to spend some time focusing conceptually on what we are looking at before moving operationally. For example, if the harm to the public health system is, for example, that it costs more or the resources aren't there, that's important. But, that isn't really, I don't think, the criteria by which we should be making -- it reminds me of my work on the U.S. Preventive Service Taskforce, where the question was, should you do depression screening or not. People said, well, we don't have a system in place but identify people with depression, they can get appropriate treatment. We on the committee at that time said, well, if there's evidence it's a good thing and having a system in place would improve outcomes, we should still recommend it and basically force the system to accommodate. So, that's why thinking about, really, what is the public health impact, I think requires some ever to say, will this actually result in harming more people over the population? Will those kinds of conceptual work, which I don't think has been done yet --

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No. No. A follow-up. This is Coleen Boyle. Just a follow-up to a Charlie mentioned. We are all being drawn to think more on return on investment. So, I don't know if this is the way to think of this. But, last time with Pompe, I was a bit surprised that the focus was on the public health side, unreadiness of the system to carry out the mission, so to speak but not necessarily the public health impact, I would consider more of a return on investment. I feel like there's a big leap on your question 10, here, in terms of the number of children and the recourse. There's a lot of stuff in between those two, okay?

In the interest of time, I'm going to continue to go through and when we get to key question 10, then, the floodgate is going to open, too. Next slide, please.

So, treatment and long-term follow-up. This gets to the issue. So, the standard of care treatment strategies for the different forms of MPS 1 and the clinical guidelines, whether or not

they are available for the long-term follow-up. In terms of the benefits and treatments, you'll see that gets discussed in a second. So, if you can go to the sixth.

We have intermediate outcome measures. So, what intermediate or proximal outcome measures to the biomarkers. Functional tests can be used to monitor and evaluate the status of MPS 1. The interventions for MPS detected through newborn screening lead to improvement in intermediate measures compared to the usual clinical detection. And, other than the age of initiation, what other factors modify the effect of treatment on the intermediate measures?

If I can go to question seven. If there are issues of primary health outcome? Just like everything else, this kind of -- there is no super distinct line between the different types of outcomes. So, I don't want to quibble on intermediate or primary or secondary health outcomes. I just want to make sure we are thinking through all of them. So, what are the most important primary health outcomes related to treatment of each form of MPS 1 identified by usual care and newborn screening. Other than the age of initiation, what factors modify the effect of treatment on help primary outcomes? How strongly our intermediate measures associated with primary outcomes to the intermediate measures to get the time course of the primary health outcomes? That is the strength of association between those. And, what influences the association between intermediate measures and primary outcomes?

Key question eight on the next slide, please. Again, here, you can quibble with something if it's primary or secondary. This is how we divided it up. What is the quality of life, over time, associated with the different forms of MPS 1 when identified through usual screening? Newborn screening? What are the family or care giver impacts over time associate with different forms of MPS 1 identified through usual care and newborn screening? The following up of the family side of things.

Question 9, benefits and harms related to treatment and long-term follow-up. Do interventions for MPS1 when detected through newborn screening lead to improvements in primary or secondary outcomes, compared to clinical detection? Or, worsening of the primary or secondary outcomes compared to clinical detection? Are the strategies that can improve these benefits or decrease or delay those harms? And to what degree does improvement in the primary or secondary outcome for MPS 1 lead to another outcome that may be considered a harm? So, depending on -- some treatments can take you from having one chronic illness to another kind of chronic illness. Bone marrow transplantation.

Here's question 10, the one everyone has been on the edge of their seats.

Question nine? Can we ask move back one?

I think that, like it only addresses people who have confirmed disease and intervention and it envisions the possibility that an intervention could make something worse, which we hope is not likely, but you've got to consider it. What I don't see anywhere in their is the harm from a

false positive newborn screening? And, I saw that in the original model and I would have expected it.

The harm for the false positives were in whatever that key question was about the diagnosis process.

It looked like the psychosocial. It could be that some people actually don't need treatment because they don't have disease. I would have expected that as question nine.

We can talk about this maybe later. The way I envisioned it, if you test positive, than the diagnoses test, one way or the other, is going to be definitive -- in terms of excluding or including the condition. It's probably true for MPS 1, but may not be true for other things.

[Indiscernible-low volume]

Right. That's where it gets to the different forms.

Okay. I want to make sure we get to question 10 before people pull up their tents.

So, again, I look for -- forward to looking -- working with Dr. Lorey to expedite some of these things in the different areas. This is probably -- I do want to talk about MPS 1 -- this is just our preliminary thing. Newborns are projected to be affected by newborn screening for MPS 1 and may require either short or long-term follow-up services for any forms of MPS 1, including true and false positive cases and true and false negative cases. What resources are required to ensure readiness and feasibility of state NBS training programs to adopt screening and follow-up services? This is where Dr Boyle was talking about. It's too big of a leap and we need to have that in other questions. In the interest of time, I won't make everyone work through that exercise.

What resources are required to ensure capacity of health service delivery systems for short or long-term follow-up resulting from expanding newborn screening? So, that gets to having all those things in place for diagnosis, treatment and follow-up, and with the availability and accessibility of required screening, diagnostic and treatment services? So, you know, again, I think, as I reflect on it, it's still a bit too high of a level, in the way that we've done this for all the other kinds of ways things can play out in newborn screening. You just need to -- we just need to drill down there. I tell you, why don't I -- I do want to talk about MPS 1. [Indiscernible].

Don Bailey. I don't know if it's the last word. First, thank you, Alex, for the thought that you have put into this. I think this helps advance the discussion in many different ways. It makes me feel both discouraged and hopeful. The discouraged part of it has to do with our task with our subcommittee, which is developing guidance for the nominators, and it reflects one of the challenges we've been having that is kind of the evolving nature of our guidance, and how we can provide something that is clear as we go through these changes. Not that I'm opposed to them, but I'm just reflect on that particular challenge. Then, understand the advocacy groups

and how it might be frustrating to them to see that we keep thinking about this, too. On the other hand, it makes me hopeful because these are providing more details and clearer guidelines, I think, that the nominators could attend to. I do think -- I was in mailing back and forth, I think this fundamentally impacts what we were planning to do and our guidance document. So, ultimately, I don't know if this is something the committee is supposed to vote on and endorse, or how we go about that. At, that will affect this. If we had a short paragraph under each one of these for the nominators about what we mean by that question, that's ultimately what would be very helpful.

Just a quick point. Whether you might pull out -- I think this is embedded in bullet three, here, which is professional education. Make sure that primary care providers and others have adequate education to respond to and fully implement a system or, whether they have capacity to provide education for the care providers.

It's Chris Kus. I guess the question I have, is in no way you are answering this for a national system. I suspect if you went to different states and asked them to answer it, they'd have different answers to this. What are you thinking of?

If you remember what we did last time, we tried to pick what we thought -- again -- this is – I thought Jelili and Susan Tanksley did a lot of this work, a really good job. We picked a representative state in partnership with our liaisons at the time. You are right. There is always going to be tension between what's happening at the national level and what's happening at the state level, and it’s just not feasible to address these things with each state. So, I think, again, where owing to be stuck looking at representative states. I don't even know if any of it makes sense, per se. I guess at the end of the day, what I'd like for the advisory committee to have, is to be able to understand what the range is that's out there.

My question is related, but first I'd like to follow-up and say that I'd forgotten about the representative states, so that makes sense. If most states are able to, but some states are not, that comes back to the point we were saying earlier. If the science supports it and the treatment is possible, but some states just aren't set up to deliver it, at some point, do you want to push -- it comes back to the equity. My question was sort of on the same principles. This is the healthcare system. I think that question 10 is addressing public health, but I think the healthcare system and public health are not the same thing. I think some of these questions are directed at, what is the professional capacity work in some broad sense, workforce comes back to public health. They are all interrelated. I think it needs to be, as you work on that split out, the healthcare system, there's healthcare delivery system, the workforce, the professions. I would split it.

I think that's a great suggestion, in terms of -- the other thing I want to remind everyone, back to your comments about having to make a decision about whether or not to push things. The great thing about being in the review workgroup is we don't have to make decisions. That's it's our job to let you know what's going on. Regardless of how good the report is, we are still going to be called to come up with a solution.

Comment? Question?

Getting back to the public health impact on Pompe. There are different ways you can ask that question. Really, the way that survey appeared to be worded, was, do you think you can do this? Do think you can accomplish this? The results seemed pretty positive. And yet, my survey, with the state directors that are doing -- actually doing the work, was a little different. Do you think this fits the new screening criteria? Is this ready for prime time? It was 100% no. So, it's who you ask and it's what question you ask.

All right. I think it's exactly right. I agree with all the comments he said. I think we have to really drill down and find out what it is that we are asking. So, we are going to put you to work. [Laughter]

Dieter Matern, the other thing that might change in the readiness feasibility issue, if the secretary recommends it to be included in the RUSP. MPS 1 will be much easier for all of the states, because the platform that they would choose for Pompe will be the same one for MPS 1. That might be another issue you have to consider.

Excellent point. So, I'm going to steal the floor --

I just want to make sure everybody is speaking up.

Thanks.

[Indiscernible-multiple speakers]

I think these are very important questions. How you ask the question, what questions you ask, which is a different way of looking at public health impact in the literature. It's really a whole new field. So, I think you were successful in having a series of meetings around to get a condition review criteria developed by an expert group and brought to the committee, go back a little bit. There were a series of group's that helped develop it. I think you can do the same thing here. You, I'm not sure you, personally. [Laughter]

Yeah. You would suggest like the same way we half a day and have meeting, that that's part of -- the powers that be, sitting to my right.

I'm going to just very quickly talk about MPS 1 and then I'd like to revisit some of the issues. Next slide.

You can look at that and admire it for second. The next slide.

Okay. So, we did hold our first technical expert panel. We were fortunate to be able to find the time to get all these individuals on the call. Dr. Burton, Dr. Clark, Dr. Dixon, Dr Muenzer, and Dr Wedehaze, nominator of the condition. Next slide, please.

The aim's for the first call, which we just recently had, would help us to understand MPS 1 better, to refine the case definition, to talk about what happens with usual care, the screening and the diagnostic process. To review what's currently done, in terms of treatment and clinical management guidelines. From there expert perspective, benefits, limitations, harms, and so forth to begin the process of identifying key informants and other sources of information. As is typical with the case of the technical expert panel, they were very energetic and had a lot of good ideas for us. We will be holding other teleconferences with those groups and others, in addition to the individual level interviews we hold with people. It's always tremendously interesting. So, if I could have the next slide, please.

For those of you who are less familiar with MPS 1, it's an autosomal recessive lysosomal storage disease that comes by the deficiency one specific enzyme, IDUA. It's a progressive multi-system disorder. Historically it's been divided into three syndromes — Hurler, Hurler Scheie, and Scheie syndrome. Like all the conditions that we look at, there's really a spectrum and there is no clear delineation between the forms. Currently, the characterization of the condition is really based on presentation, severity and treatment options. The severe form which encompasses Hurler and the attenuated forms, which are Hurler-Scheie and Scheie, there is an overlap between all of this. For purposes of this report, we are going to talk about severe and attenuated forms of the condition. The severe form is associated with infants normal at birth, and develop symptoms the first year of life. It rapidly progresses with significant central nervous system (CNS) involvement and severe cognitive deficits. There is a progressive skeletal dysplasia. You can see below, an example of typical natural course of the position with nonspecific problems in the first year of life and then, worsening problems and death in early childhood. Next slide, please.

Here is a description of the attenuated form, which again, its heterogeneity. It's heterogeneous presentation with onset and severity being fairly variable. It has symptoms before five years of age. It's slower and has more variable progression than the severe form. It's a multi-system disease, similar to the severe form. But, it has variable CNS neurological involvement, cognitive deficit, hearing loss, cardiac valvular disease, joint manifestations. It's clear that this is difficult to diagnose when children first develop symptoms. It's highly variable lifespan. Next slide, please.

So, in terms of the epidemiology, I think the best epidemiology we have in the United States comes from the work that Dr Scott did looking at anonymous dried blood spots. From a sample of about 106,000 anonymous dried blood spots, he used the screening method, which is based on tandem aspect. Based on the enzyme levels, who can't distinguish the forms. So, the numbers I are -- I'm about to show you are not the same as population-based epidemiology. The overall estimated probability based on that study was about one in 36,000. The positive predictor value of the mass-based evaluation he did was 33%. Again, there's quite a confidence

interval, because of the fact that only about 100,000 dried blood spots were evaluated and has a false positive rate of about one in 18,000. Again, you can see there's a fairly broad confidence interval. Next slide, please. This is from the Pompe Disease Registry, from a report published in 2012. Genzyme keeps the MPS 1 Registry in the same way they did with Pompe Disease. I've already spoken to those representatives from Genzyme and they've agreed to help us explore that data set, so we can better understand what's going on with detection, so that we can better estimate the value of early detection. The numbers involved are years of life. So, within the registry, of course, which these things are always a little bit biased, based on who ends up in the registry, they age of onset for the severe form is about six months of life for attenuated MPS 1. It's around two years for the Hurler-Scheie and about five years for the Scheie. In the data set they have things distinguished that way.

You can see -- if you just read across the rows, you can see the average age of diagnosis and treatment initiation. I said average, actually median, I apologize for that. Next slide, please.

What I'd like to walk through very quickly, is the process of how screening might work. We began with newborn screening of dried blood spots that had -- where you would measure the enzyme activity for IDUA, that's the enzyme deficient when you have Pompe Disease. There are different ways of assessing the enzyme level, whether that be through MS/MS, Lumina, or Digital Microfluidisc, whatever, there's different ways of doing it. If you have Low IDUA activity, next slide.

It's a miracle that the animation works. Then, the initial step is to confirm that the enzyme activity is low. You can see that in variety of sources, blood, fibroblast. From what the experts told us, in blood, it's quite easy to measure. You also need to, at some point, assess the urine, the Glycosamioglycan (GAG). If the GAGs is not elevated, that's a way to elevate pseudodeficiency which can occur, but it's quite rare with MPS 1 or false positive screen. Then, elevated GAG levels would, in combination with the confirmed low IDUA activity, would confirm MPS 1. And then of course, a mutation analysis. This can either be done stepwise or the experts said when they were faced with a baby with a low enzyme activity level they would just stuff all at once.

I don't have data I can present to today, in terms of the number of mutations that are known and the genotype correlation. But, from the experience of the experts, there are a lot of new mutations being found all the time. One can't necessarily predict the course based on mutation analysis alone. Next slide. Lucky again. So, just to summarize the MPS 1 would become confirmed with a low IDUA activity, elevated GAGs levels, typically from the urine, that can be the blood, as well. Then, mutation analysis that can help, but not always tell you what the exact type of the situation is going to be. Next slide.

In terms of treatment options, for the severe form, the treatment is stem cell transplant. The important thing to realize, even though there is enzyme replacement therapy, the enzyme replacement does not cross the blood brain barrier, which is why enzyme replacement can't be used for the severe form. The experts out there, earlier in the disease course, would be to

better outcomes. But, there's a fairly big – figuratively relative -- in terms of the window for beginning the transplant up to even three months of age. Of course, treatment with stem cell transplantation is associated with mortality. That, of course, the morbidity associated with a stem cell transplant. The experts said the enzyme replacement therapy can be used before the transplant to stabilize infants. But, the studies are still under way to evaluate what the role of enzyme replacement therapy is before transplantation. But, the babies who are transplanted do not need to continue on enzyme replacement therapy. Next slide.

So, for the other form of this, there's the enzyme replacement therapy, which is recombinant form of the inactive enzyme, it was FDA approved in 2003. It's indicated for attenuated MPS 1 and severe MPS 1 when transplantation is either declined or for whatever reason contraindicated. The treatments, again, like all the other enzyme replacement therapies, we talked about his lifelong. It requires weekly IV infusions which is well tolerated, according to the experts, with occasional mild infusion reaction. We already talked about the crossing the blood brain barrier. In the issue of time, maybe I will just go ahead and skip to the next slide that begins -- skip please.

MPS 1 is detected earlier through newborn screening. It's hypothesized that early initiation of treatment will improve outcomes. There's also some thoughts for the attenuated version, that maybe you could later decrease enzyme replacement therapy if you do enzyme replacement therapy earlier. There’s questions about the timing of treatment for pre-symptomatic patients. You can hear that in the call that we had with the experts. But now, this sense is that enzyme replacement therapy wouldn't be started until there was some sort of signs and symptoms. Exactly what signs and symptoms would precipitate the start of enzyme replacement therapy, was a matter of debate, in terms of level of threshold. Next slide, please.

So, we have begun the initial literature search, just to share. There were about 2,000 publications across the three data sets related to MPS 1. See if you can skip ahead two slides.

Perfect. You can see that we are going to do our traditional grey literature search. As I mentioned before, we've already spoken to Genzyme about the registry. Next slide, please.

Of course, we will be talking to the states that are involved, and screen that activity around MPS 1. Of course, we are going to have follow-up, at least one more follow-up technical call and the individual key informer calls, as we usually do. So, next slide.

In a sense, we've already talked about our next steps in terms of refining the questions. So, I won't belabor that point. But, for the kind of data that we know we need to get, that something as an impediment to us is beginning to extract the data. I'd like to stop right there. The next slide.

Alex, thank you for an excellent and thorough update. I think it shows that, in addition to addressing the specific condition, there is ongoing work on the refining the public health impact and I think we are getting a lot of input on how to do that, as well as having further refined the

process, in general. So, I think that's very productive. Any brief comments? We need to get the next presentation started.

If none, thank you for the update and we'll go forward.

So, the next is a presentation on whole genome sequencing in newborn screening. Dr Brower, are you on the line?

Operator, can we make sure Dr Brower's line is open?

Her line is not open -- connected. If you are here sitting with someone else, please press star then zero. Again, I don't see that she is connected.

She is dialing in at the moment. Okay.

Clearly, I think you've got the process under way in a very nice way. I think that we are looking forward --

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This is Doctor Brower.

Great. Thank you.

Amy, we can hear you well. Let me just introduce you and we will let you get started.

Thank you.

Okay. Doctor Brower is well-known to the committee. She's presenting to us today on the genome sequencing. She serves as project manager on the National Coordinating Center's Long-Term Follow-up project at the American College of Medical Genetics, and also works with Aurora Health Care on genomics education and clinical research. She has a background in medical genetics and bioinformatics, was a member of the human genome project team. She's presenting this for Mike Watson, who is unable to be here today. Amy, we appreciate you doing so and we will turn this over to you. Your slides are up. All you have to do is ask that they be advanced when you are ready.

Great. Thanks -- thanks to the committee for the opportunity to present on behalf of Mike Watson and myself. The practice of medicine is increasingly being formed by genomic discovery. The committee thought it would be a good time to introduce you to some of the basics of genomics and newborn screening that are becoming [Indiscernible]. Next slide.

We will go over today some basics of the genome, just a reminder of the basics of the genome that you learned during med school and over the last few years. If you've been keeping up with the literature and the professional journals, as well as CNN, you know genomics is a hot topic, and something people are continually trying to grasp the impact for healthcare. There's been

no game changers yet, but we are waiting for that to happen. I will go over some of the basics of sequencing, the use of the genome and exome sequencing, and we will talk a little bit about the research in newborn screening and sequencing. Next slide.

Over 50 years ago, Dr. Avery and his colleagues discovered the DNA molecule. At the time, they thought it would be very revolutionary, and we know that we celebrated the 50-year anniversary of the discovery of DNA just a few years ago. We celebrate the 50th anniversary of newborn screening this year. Next slide.

We think about the genome, we really think about all of the genes and all of the regulators that are spread across the genome. We think about genomics, it not just one gene at a time or what we think about as one gene, one disease with typical [Indiscernible]. We are really thinking about the impact of all the genes, all the regulators, or the on/off switches across the genome. It's important to point out that just 2% of the 6.4 gigabytes per cell we get 3.2 from our mothers, 3.2 from our fathers. Only 2% of that is actually coding regions that code into genes. But we all know that each gene can code a variety of different types of protein products. So, that's where we get the diversity in the human genome across the board. Next slide.

Every living thing has a genetic blueprint. This is a set of instructions that tells the body how to grow and how to develop. For humans, the instruction manual is called the human genome. This blueprint is packaged into every cell, and organized into long ladders of DNA that form chromosomes. As you know, we each have 23 pairs of chromosomes, one from our mother, on from our father and each chromosome contains several thousand genes which code for proteins, the building blocks of tissues, muscle, blood cells, hair cells, human life, essentially. Genetics determine simple things like eye color and complex things like cancer. Next slide.

Just a reminder on the size of the human genome, 3.2 gigabytes -- IT technology terms, as well — 3.2 gigabases. We have the ability to also detect [indiscernible] across platforms. If you click through, one more click on the screen. Then, another click and another click. That gets you familiar with the kind of terminology you will be seeing, as we come to the committee with more and more reports of newborn screening and genomic outcomes. As we said, every living thing has a genetic blueprint. There's no normal genome sequence. Humans are very similar at the DNA sequence level. In fact, we think that 99.6% of the base pairs are identical from one person to another. But, we know there are differences. About one every 300 or 3,000, depending on the latest research that you are looking at, for any two individuals could differ by 24 million base pairs. Those are, essentially, what we look for when we do to genomic sequencing in the newborn period. Some of the differences can cause disease early in life and some differences can cause disease later in life. Some affect the way we respond or fail to respond to medications. Some differences do nothing at all. Scientists and clinicians around the world are working to understand which differences are important and to understand the diagnosis and treatment of disease. Next slide.

If we think about 3.8 million variants per person, and we applied genomics in newborn screening, we are essentially having 3.8 million test results for each of these newborns. That's

part of some of the projects that are really groundbreaking that NIH and NICHD and NHGRI have now funded. . We will talk about it at the end of the project. Next slide.

Remarkable advances have been made in understanding of human genome's contribution to health and disease since the publication of the sequence of the genome almost a decade ago. Also, an Internet click away is a rapidly growing catalog of a collection of 1,000 genomes. The goal of the 1,000 genome project is to find the most genetic variants that have frequencies of at least 1% in the population study. This goal is attained by sequencing many individuals lightly, that means coverage, if you do coverage -- one X sequencing in and the person means you've done one-time genome sequencing across all their chromosomes. If we go to tenfold or twentyfold in sequencing, we've resequenced them, 10, 20 times. The more you sequence, the more chance there is that you'll likely to find genetic variance. Unfortunately, we don't know what this all means. The 1000 genomes didn't include any phenotype or clinical data. It only captures sequence variations and information on how frequent those are in the populations that we are studying. Next slide.

Just to remind us, there are many different -- not just the human genome, cancer also has its own genome. In cancer cells, small changes in the genetic letters can change what the genomic word or sentence means. The change letter can cause the cell to make a protein that doesn't allow the cell to work as it should. So, change in the cancer genome really influences cancer onset, progression, response to therapy, prognosis, relapse, response to different types of stem cell transplants and other things. So, looking at the genomics is not just important in newborns or in humans, but also across the complex landscape of human malignancies. Next slide.

We believe that genomic testing will play a role across lifespans, from the simple blood test in the first days of life, to identify treatable diseases that cause disabilities and deaths, to tests to help diagnose childhood diseases, tests before pregnancy to estimate the likelihood that a child would have a genetic disease, and tests later in life to determine which drugs to choose or which treatments to applied to individual patients. Test may be used to identify susceptibility to disease even before science -- signs and systems have become noticeable or measurable by other test and two on certain populations, whether defined by gender, age, race or ethnicity that put a person at increased risk of disease. Currently, over 4,000 genetic and genomic tests are available, but only a few dozen have been recommended for routine testing. The majority of these tests are recommended for women, and that's something that we will pay attention to as we get to the newborn screening story. The next slide.

There have been rapid advances in sequencing technology. When I was part of the Human Genome Project, we really used first generation sequencing, the classical sequencing with Sanger and Maxam. Now, we have two other options called next generation and third generation sequencing. In traditional sequencing, each reaction provides approximately 1,000 pairs of DNA sequence, about 600 base pairs long, and we can typically run 100 reactions in parallel. In contrast, next-generation sequencing takes advantage of miniaturization and automation, and hundreds of thousands to millions of DNA fragments in parallel using extremely small amounts of chemical agents per reaction. A single sequencing run with next-

generation technology can yield more than 100 gigabytes, which is 100 billion pairs of DNA sequences in a matter of hours or days, depending on the technology used. Next slide.

Pretty quickly, just to remind you what classical sequencing looks like. You can see the traces, the T's are red, the G's are black, the A's are green and the C's are blue. In general, this is what we used to do when we used to read classical sequencing and get individual sequence reads. Next slide.

This reminds us about a vast improvement with next-generation sequencing and the cost decrease. So, we are quickly becoming close to the $1,000 per exome cost and the $5,000 per genome, or the current cost, of sequencing for using next generation. The next slide reminds us that you don't have to look at the whole genome. In fact, you can just look at the protein coding region. This is called exome sequencing. When we talk about genomic sequencing, we really sequence head to toe every chromosome, every piece that we can interpret. With exome sequencing, we only look at the coding region of the genome. Next slide.

This is the first example in 2010 of using -- successfully using whole exome sequencing to identify a gene in a very rare condition. This is Miller's syndrome, a rare condition that affects the development of the patient's limbs. The severity in this disorder varies on the detected individual. By using whole exome in a few targeted families, researchers from the University of Seattle, University of Utah, and Johns Hopkins University were able to identify the gene that was involved in this particular family and also in other families with Miller's syndrome. Next slide.

Quickly coming on board, is third generation sequencing. It's a single-strand sequencing and requires no amplification of the DNA. Several chemistries are being tried out and it's still limited by interpretation. You may see some reports of third-generation sequencing as you hear more about newborn screening and genomic sequencing. Next slide.

I think this is one of my favorite slides. It shows -- I will just read it -- I think you should be a little more explicit here in step two, because on the left we have a lot of things that happened and in the middle, then a miracle occurs, and on the right, some more things that happened. We think there's a lot we need to figure out to get to the level of $1,000 personal genome. But also to be able to interpret that and to change lives. Next slide.

So, this is a reminder that there are many applications that we think will be used for next-generation sequencing. You can look at the type of sequencing, whether it's de novo, we don't know what we are looking for when we have a new flu strain or new virus that we might be interested in, all the way down to RNA sequencing, where we are interested in gene expression and which parts of the genome are expressed at different times. Next slide.

There are many different applications work current clinical uses of genome sequencing and exome sequencing. We wish that we understood more about how they're going to be used in the future so we can prepare. Right now, there are diagnostic panels, multigene panels that

target cardiomyopathy and hearing loss, for example. Nonspecific phenotypes in undiagnosed patients and also screening for carriers, noninvasive prenatal testing and preimplantation genetics. Next slide.

Current uses of sequencing and newborn screening, we can see that there multigene diagnostic panels that screen for different physiological or phenotype based screens. These mostly occur in the second-tier testing and newborn screening or the diagnostic phase, if we have a child that fails the initial newborn screening test. Next slide.

So, this is Mike's slide. I was a member of the Human Genome Project. I don't know if I have guilt. But, there's $3 billion plus the genome project costs the taxpayers and one million-dollar interpretation. So, now we are trying to figure out what can this great science do for us and how do we apply that to change lives and improve healthcare. Next slide.

There is a new project you all I'm sure have heard about, genomic sequencing and newborn screening disorders. Next slide.

On December 13 and 14, two years ago, three years ago, NICHD, NHGRI, and the NIH Office of Rare Diseases Research sponsored a workshop called Newborn Screening in the Genomic Era, Setting a Research Agenda. The purpose of the meeting was to identify elements of the trans-NIH research agenda that would lead to the application of new genomic concepts and technologies to newborn screening and child health. Next slide.

Out of this workshop came RFA's looking to support and adapt new technologies to newborn screening and genomics. The NBSTRN is working to support the use of this type of sequencing in the newborn period. We have a ELSI workgroup. We have a VRDBS, which is a virtual repository of dried blood spots as a source of true positives. We have informatics tool that allows longitudinal data collection and aggregation of clinical data, so that once you do the genome sequencing, you can follow how these children are doing and see what might play a role in impacting the different genomics findings. Then we have finalized development of what we call harvest, an integration engine that allows clinical data in LPDR to be integrated with the new findings from the genomic sequencing. Next slide.

The biggest challenge, obviously, is how do we interpret the changes that we find. If you remember from the slide earlier, we said at we would find at least 3.4 million changes between each one of us. What do we do when we want to interpret that? How do we apply that to normal developing infants, or to infants that have seen health trouble. How do we make the leap between what we're finding in the genome or seeing clinically? Next slide.

Can we depend on our current in silico or computational analysis tool? As we look across these tools and begin evaluate them for use in NBSTRN. We are looking to see if they all agree with each other. Can we rely on a composite, and are we really of playing in the cutting-edge if an emerging science as we tried to figure out what the different tools and resources need. Next slide.

How do we decide what's normal? So, we have many, many different databases that are online, that house genomic and genetic variation. NBSTRN and ACMG are part of a clinically relevant variant resource (CRVR) project that will work to catalog and to create curation on the genomics findings. You can begin to understand what this particular based care team needs. Does that happen in the genes? Doesn't happen in the regulator? What's the percentage across different populations that we find this mutation? And how do we use that to interpret things clinically and improve lives? Next slide.

There's also the issue of what we do with secondary findings. This is things related to mutations related to late onset disorders, whether or not medical intervention or lifestyle intervention is available. Identification of carrier status for recessive disorders and variants related to drug metabolism. There are a lot of issues to think through. Next slide.

We are just going to give you a brief introduction to the new NICHD/NHGRI newborn screening sequencing program.

They wanted to look at many more diseases associated with many more markers. Not all variants were well enough understood to be used in newborn screening and targets. They were hoping to shift some functional screens to a second-tier testing to identify those most likely to cause disease. Next slide.

There were three main components of the program. Genomic sequencing and analysis, research related to patient care, and ethical legal social issues in the use of genomic information and the newborn period. Funding was $25 million over five years. Let's take a quick tour through these next slides.

This first one is from the PI Doctor Robert Green and Dr. Adam Beggs from Brigham and Women's Hospital in Boston Massachusetts. Each of these projects has a different goal for using newborn screening or exome screening in the newborn. These PI’s are looking at 450 newborns and will follow them throughout the course and see how well they do. The next slide.

The next grantee is Dr Stephen Kingsmore from Children's Mercy Hospital, Kansas City Missouri. He will use genomic sequencing and exome sequencing in newborns NICU to see if they can reduce the time to figure out what's wrong with the baby and to see whether or not it makes a difference for helping to get through the diagnostic odyssey or coming up with diagnoses a little bit sooner. Next slide.

Grantee number three is Dr. Robert Nussbaum from San Francisco. They have some interesting proposals, they were partner with the California newborn screening program to assess 1,400 children, previously screened by classical newborn screening, to see what this contributes. So, also adding a genomic component to the SCID training being done at UCSF and they will provide pharmacogenomic testing to reduce adverse drug events. Next slide here.

Our fourth and final grantee, Dr Cynthia Powell and Dr Jonathan Berg at the University of North Carolina at Chapel Hill. They'll sequence the entire genome of 400 infants, and determine what useful clinical data will be acquired through these tests. They will also focus on infants with other conditions like PKU, CF, or other errors of metabolism and also add a multicultural interest to their efforts so we can make sure they understand how this plays out across all different race and ethnicities. I should point out each one of these projects has a big focus on ethical legal social issues and will learn more about those as those programs become online. Next slide.

There's other NIH related research, the Clinical Genome Project that includes, as I said before, the Clinically Relevant Variant Resource and the U41 groups effort to capture patient's variant and clinical data for analytical and clinical consideration by the CRVR. There's Clinical Sequencing Exploratory Research, the program to assess integration of sequencing into clinical care, and there's a Return of Results Consortium, assessing issues associated with the return of results of different types. Next slide.

We know there will be a lot of questions. We ourselves have questions about how to use genomic sequencing in the newborn period. This is a quote from the Twila Brase, the President and co-founder of the Citizens Council of the Health Freedom in St. Paul, Minnesota, and I'll let you read that, as they say, that we're all looking forward to understanding more about the application of genomic sequence in the newborn period and how best to improve the healthcare of our newborns and to protect their privacy and other issues.

So, the promises are to improve the ability to make molecular diagnosis, but to understand the range of genotypes associated with individual diseases, so that we can guide individual patient care and provide options for family planning. We anticipate, and this isn't a big guess, that witness open new doors and new avenues of research and increase our understanding as human genetic variability, and with that I can take questions, and thank you for letting us present today.

Thank you for a very exciting and very well organized presentation that has shown us kind of a window to the future. So let's kind of open this discussion but any questions or comments from the committee?

This is Kathy Wicklund, thank you for that presentation. I just had a quick question about the grantees. Are any of them partnering or working with Public Health Departments just in thinking about how this could impact Public Health Departments?

Well, Dr. Nussbaum at the University of California San Francisco is working directly with the Department of Health in California and I'm sure that at UNC, they will also be working with their Public Health Department. These other two didn't particularly call out public health as working with them, but we could definitely ask them and get back to you on it.

Thank you.

Hi, this is Natasha from Genetic Alliance. Can you guys hear me?

Yes, we can hear you go ahead.

Okay, great. Thank you, Amy for a great presentation. I just wanted to let everyone know, if you did not know, Genetic Alliance had a summit on August 20th called Beyond the Bloodspot that covered emerging technologies, and a key piece of that was talking about sequencing and the newborn screening period, and it had industry representative researcher, State newborn programs, so it's just another resource out there for people who would like to dive in a little bit more on these topics. In the comment section, I put a link to the materials from that meeting. But again Amy, thank you very much for bringing this to the committee.

Great, and thank you for reminding us about that important meeting. We also thought, as a follow-up for the committee, if it would be helpful that maybe on a monthly basis or at least quarterly we could send you things like Natasha just highlighted, that you may want to join in and learn more yourself. So we in the genomics community find out about efforts to engage or efforts to discuss these principles we would be happy to give you guys that information if you'd like to consider it.

Kellie and then Jeff.

Hi Amy, great presentation. Without delving into each grantee and their plan, do they plan on using traditional sequencing to validate or confirm anything that they find, using this view as whole genome sequencing, given that I've even heard concerns from clinicians about false positives hinting at false negatives with the new technology, unless we really make sure that what they're receiving from this new technology is the real deal.

Yeah, the analytical validation of the next generation sequencing and the whole genome sequencing is one of the big key components of this project, so in looking at does the test tell you what it's supposed to mean, and each of the programs did include a robust look and analytical validation, including resequencing, using traditional sequencing as well as genotype test to confirm when they find a particular mutation and a particular gene and a particular patient.

Thank you, Jeff and then Andrea?

This is Jeff. Thanks, Amy. One of the things that came out of the NIH conference from a couple years ago that you referred to was making a distinction between newborn screening and, or sequencing newborns and the newborn screening, it's not quite the terminology but I think what is concerning me with the discussion is the blurring of the line between the potential utility of this technology for sick babies, or kids who have conditions detected by newborn screening, and really thinking about it as a primary screening tool. It just seems to me inconceivable that the whole genome sequencing, whatever achieved status as a primary

sequencing tool, and I think one of the things that, at fairly simple level, we talk about thousand dollar genome but that's a thousand dollars for the most part for the reagents as opposed to the interpretation, and if you're sequencing every baby, pretty much every baby needs some sort of interpretation. So the absolute scale of population based newborn screening is far beyond what society has been willing to commit for anything in the public health arena. So, from my perspective, very creative to think about the role of sequencing of newborns, but not particularly responsible to be thinking too seriously about this as a primary screening tool.

Yes, and thank you for that distinction. I think these grants will as they go over their five year course of the study will learn more about that and I think it is an important distinction of the sequencing of newborns versus newborn screening sequencing, [LAUGHTER]

If I could make a comment, this is Melissa Parisi from NIH, and this initiative was not designed to completely shift newborn screening into the sequencing realm. It was really designed to be a pilot study, to really try to determine what are the factors that might play into doing whole genome or whole exome analysis in newborns, and by trying to incorporate all three aspects of what we thought were the major elements, the sequencing technology is obviously important, the clinical paradigm and the indication for doing the sequencing and then of course the healthy related and public health issues are also very important components. So, just to clarify that we aren't proposing that newborn screening become newborn sequencing, but that this is really a pilot program to test these out in some very controlled settings with a lot of very smart people putting their heads together. So we're excited about it and looking forward to some of the outcomes, so hopefully we'll learn quite a bit from this program.

I just wanted to follow-up on something similar. I can give you a little bit of information on the study, for example, like one part of it will be something like 3,000 spots from the California program that consist of known cases, false positives, false negatives, and they're all metabolic, and then there's another part for the Center for [INAUDIBLE] the consented part of unusual immunological patients of hers [INAUDIBLE], so they are going to be looking for the modifiers, anything that might conceivably help the false positive situation, anything like that but, as you said, not a replacement.

Additional comments? Questions? Carol?

I think that it's spectacular that the work that's being done, and I think the point just made that this is not an effort to replace functional newborn screening, but to understand the use of the technology in newborns and children, and especially keep in mind that I don't think we need to react to this just in the context of newborn screening because this is not a newborn screening committee. This is a committee on Heritable Disorders in Newborns and Children and this is an important thing to understand. With that said, to the extent that people might go to newborn screening using primary sequencing, we have been through that discussion with mass spectrometry and the question of, do you report everything you find or what do you filter? If you don't filter, then there's no relevance to the work of the committee saying, for what diseases should we screen, because you potentially are screening for everything. There is also

some, and it was an incredibly wonderful presentation and there's some important nuances that people I think need to appreciate. Among them, if the screen is positive and the DNA is negative, we don't know where all of the regulatory sequences are, and the functions still should trump the DNA if the functional testing is positive. Another is, if the DNA is positive and the functional test is negative that's still not a guarantee you don't have it, it could be something that could present later. Something we discussed yesterday was myopathies as a reason for not tolerating exertion and those are, among other people, the carriers for CPT and other interesting disorders, and one of the questions is what filters do you use, and the people I talked to that run these labs point out that when you collect genomes from thousands of individuals who are healthy, then there's a carrier frequency for CPT1, and those are healthy, and so that's a polymorphism, a normal variant so you look right past it and a lot of the filter also not taking into account. They are looking at polymorphisms but not necessarily known diseases. So I think this is an incredibly complicated issue and I think this committee should not be looking at it just in the sense of newborn screening, and not to try to do things that NIH can do better or CDC can do better but to think about some of the public health implications would be, I think, very appropriate for this setting.

Thank you. Any additional comments? Amy, related to that? Anything?

No, I agree wholeheartedly, and thanks to everybody for giving us time today to present this introduction.

Okay, here is Don.

This is Don Bailey. So I am involved with the North Carolina project and I'll be leading the ethics piece of that so one of the big issues around all of this, of course, is return of results and what information would be given back to family who are participating in the project and I know [INAUDIBLE] already has a statement on informed consent, we'll be building on that but focusing more on informed decision-making. So how do we help families understand, as best we can, what the potential range of results could be from whole exome sequencing, and then give them an array of choices for what kind of information they would like back, and who makes what choices and the reasons why they make them and the factors associated with their decision will be a big part of our project. So we'll end up with an app that will help families think through their options but of course that wouldn't be a standalone. It could be used in context in conjunction with a genetic counselor or a recruiter who would be working with families to invite them to participate in the project.

Thank you Don. Additional questions or comments? Hearing none, thank you again, Amy for an excellent presentation. We really appreciate it.

You're welcome.

Okay, so I know that it's getting late and I think the committee has had a very productive meeting. I think that a number of important discussions and some important considerations

and recommendations for us to go forward. We had placed, at the end of this meeting, an opportunity for open discussion about future meeting topics. I think that we've already figured out some, based on what's happened over the course of the past two days, but are there any additional questions, comments, or considerations for future meeting topics that we might briefly review at this time? I know that everybody has concentrated for two days. Chris?

Chris Kus. I guess I mean just a general thing to throw out, the idea being, how do we rate our current newborn screening program, strengths and weaknesses, and how might we measure progress on the program so that you can think about how this committee could help improve things?

Good. Anything additional? Well, last chance. Okay, I want to thank everybody, especially I want to thank HRSA for preparing and putting together this meeting, and I guess under limited IP, have really put together a really incredible successful meeting. We've had been able to put on the meeting quite successfully, I believe, and I think we're all happy that we were able to meet in person. I think that that certainly helped this meeting be successful, and we again appreciate the opportunity to HRSA to allow that to happen and hope we'll be able to continue to do this on a as regular basis as possible. Want to thank the committee members for their work, the liaisons for theirs, and the public and other participants that were online and so with that, I think that we'll close the meeting and again, thank you very much.

[APPLAUSE]

Thank you!

[The DACHDNC Webinar has concluded].