The Advisory Committee on Heritable Disorders in Newborns and Children

Day Two

HRSA Meeting

Rockville, MD

November 9, 2017

9:30 a.m. - 2:30 p.m.

A P P E A R A N C E S

COMMITTEE MEMBERS:

JOSEPH BOCCHINI, M.D., Committee Chair, Department of Pediatrics, Louisiana State University

MEI WANG BAKER, M.D., Professor of Pediatrics, University of Wisconsin School of Medicine and Public Health, Co-Director, Newborn Screening Laboratory, Wisconsin State Laboratory of Hygiene

JEFFREY P. BROSCO, M.D., Ph.D., Professor of Clinical Pediatrics, University of Miami School of Medicine, Department of Pediatrics

KELLIE KELM, Ph.D., Food and Drug Administration, Ex-Officio Committee Member

DIETRICH MATERN, M.D., Ph.D., Professor of Laboratory Medicine, Medical Genetics and Pediatrics, Mayo Clinic

KAMILA MISTRY, Ph.D., M.P.H., Ex-officio Member, Agency for Healthcare Research and Quality, Office of Extramural Research, Education and Priority,

MELISSA PARISI, M.D., Ph.D. Ex-Offico Committee Member, National Institutes of Health, Eunice Kennedy Shriver National Institute of Child Health and Human Development

ANNAMARIE SAARINEN, Co-Founder, CEO, Newborn

Foundation

CATHY WICKLUND, M.S., C.G.C., Northwestern University, Feinberg School of Medicine, Center for Genetic Medicine

SUSAN A. BERRY, M.D., Professor and Director, Division of Genetics and Metabolism, Department of Pediatrics and Genetics, Cell Biology & Development, University of Minnesota

CYNTHIA M. POWELL, M.D., Professor of Pediatrics and Genetics, Director, Medical Genetics Residency Program, Pediatric Genetics and Metabolism, The University of North Carolina at Chapel Hill

SCOTT M. SHONE, PH.D., Senior Research Public Health Analyst, RTI International

BETH TARINI, M.D., MS, FAAP, Associate Professor and Division Director, General Pediatrics & Adolescent Medicine, University of Iowa Hospitals & Clinics

CARLA CUTHBERT, PH.D., Ex-Officio Member, Centers for Disease Control and Prevention, National Center for Environmental Health

LAURA KAVANAGH, MPP, Ex-Officio Member, Health Resources and Services Administration, Maternal and Child Health Bureau

CATHARINE RILEY, PH.D., MPH, Designated Federal Official, Health Resources and Services Administration, Maternal and Child Health Bureau

Debi Sarkar, M.P.H., (for Laura Kavanagh)

Scott Grosso, PH.D. (for Dr. Carla Cuthbert)

Joan Scott, M.S. C.G.C. (for Ms. Laura Kavanagh

ORGANIZATIONAL REPRESENTATIVES:

ROBERT OSTRANDER, M.D., American Academy of Family Physicians

MICHAEL WATSON, Ph.D., F.A.C.M.G., American College of Medical Genetics and Genomics

BRITTON RINK, M.D., MS, Mount Carmel Health Systems

KATE TULLIS, Ph.D., Association of Maternal & Child Health Programs

SUSAN TANKSLEY, Ph.D., Association of Public Health Laboratories

CHRISTOPHER KUS, M.D., M.P.H., Association of State and Territorial Health Officials

SIOBHAN DOLAN, M.D., M.P.H., March of Dimes

CATE WALSH VOCKLEY, M.S., C.G.C.S., National Society of Genetic Counselors

CAROL GREENE, M.D., Society for Inherited Metabolic Disorders

ADAM B. KANIS, M.D., Ph.D., US Army Consultant to Surgeon General for Clinical Genetics Department of Pediatrics, MCHK-PE Tripler Army Medical Center

NATASHA F. BONHOMME, Genetic Alliance

Jackie Seisman, M.P.H., (for Natasha Bonhomme)

C O N T E N T S

P R O C E E D I N G S

DR. JOSEPH BOCCHINI: All right. Good morning, everyone. I want to welcome you to day two of the November meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. And, I think we had a really excellent meeting yesterday with a number of really good presentations and good conversation and information coming from the Committee. So, I want to thank everybody for their participation.

I want to just also recognize that today is National Genetic Counselor Awareness Day.

[Applause.]

I certainly recognize the critical role that the genetic counselors play in the health care of the -- of this nation. So, again, thank you for the work that you do.

So, first on the agenda is roll call. So, we'll start with Kamila Mistry?

DR. KAMILA MISTRY: Here.

DR. JOSEPH BOCCHINI: Mei Baker?

DR. MEI WANG BAKER: Here.

DR. JOSEPH BOCCHINI: Susan Berry?

DR. SUSAN BERRY: Here.

DR. JOSEPH BOCCHINI: I'm here. Jeff Brosco?

DR. JEFFREY BROSCO: Here.

DR. JOSEPH BOCCHINI: Scott Gross will be covering for the CDC today.

MR. SCOTT GROSS: Here.

DR. JOSEPH BOCCHINI: All right. Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: And, then today Joan Scott will be covering for HRSA.

MS. JOAN SCOTT: Here.

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Here.

DR. JOSEPH BOCCHINI: Cynthia Powell?

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie's on her way. Scott Shone?

DR. SCOTT SHONE: Here.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And, Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: And, then for the Organizational Representatives. Bob Ostrander?

DR. ROBERT OSTRANDER: Here.

DR. JOSEPH BOCCHINI: Michael Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: By phone, Britton Rink?

DR. BRITTON RINK: Here.

DR. JOSEPH BOCCHINI: And, by phone today, Kate Tullis?

DR. KATE TULLIS: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: By phone, Chris Kus?

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Dolan?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: Cate Walsh Vockley?

DR. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: Carol Greene?

DR. CAROL GREENE: Here.

DR. JOSEPH BOCCHINI: All right. Thank you. So, the workgroups met yesterday afternoon, and today we're going to hear presentations by the workgroups. As you know, they were tasked for giving us a timeline for the projects that they have underway or are in the process of completing and begin

discussion on development of new potential topics and subjects to bring forward to the Committee so that ultimately they can get feedback from the Committee, and we would then prioritize those projects that the Committee accepted as being important for the workgroup to go forward with.

So, I think that we will hear the presentations, discuss those issues, and then make some decisions about what the next steps would be.

So, first on the agenda is update from The Education and Training Workgroup. Following the workgroup presentations and seeing how far we can go with prioritizing activities, we're going to hear a panel on the Clinical and Public Health Impact of SCID Screening in the United States.

All right. Next slide. Okay. So, first on the agenda then is the update from the Education and Training Workgroup, and Beth Tarini will provide that update as Co-Chair to the Committee Workgroup.

DR. BETH TARINI: Okay, thank you. So, my chair, Catherine Wicklund, is not here, so I will present an update from our workgroup along with Amy Gaviglio, who has been leading one of our projects.

So, the first project I'm going to discuss is the Newborn Screening Education Planning Guide, and this project -- I believe you have been emailed an electronic file for it -- is an Excel document. The reason you've been emailed that file is

because it's somewhat difficult for many to conceptualize this planning guide and may be not be familiar with this, which is a tool used in educational curriculum design.

So, the need, purpose, and scope of this project. The need is that -- and, let me just pause actually to say the two individuals who have been spearheading this effort who deserve the vast majority of the credit are Cate Walsh Vockley and Jeremy Penn, who have been very significantly involved and sort of deserve all of the credit. But, I'll take the blame.

So, the need is that newborn screening stakeholders need access to appropriate accurate and informative educational resources that meet their range of educational needs. The purpose then was to address this need by creating a Newborn Screening Educational Planning Guide, and the goal is that that guide would be used by Newborn Screening Programs and other stakeholders to develop and improve the Newborn Screening Educational Resources.

And, the scope of this guide was this -- this guide would be used by individuals looking to create educational resources for a whole host of relevant stakeholders. They would take this guide and say, I'd like to create an educational product for midwives. What should we put in it? This guide would serve as a starting point for what we believe are important but not completely exhaustive lists of content areas that should be considered to be included in that guide.

The groups are always, of course, welcome to tailor to their individual needs.

So, the model used was based on the Design of Educational Resources theory, and that's based on the work of R.W. Taylor. The goal, again, is that this tool would be used by a wide range of newborn screening stakeholders. The review process involves the E&T Workgroup and all of its diverse members, creating a list of relevant stakeholders, as well as a baseline range of content areas that may be relative to those stakeholders. And, then going through and having representative -- well, a group -- or I should say representatives from those stakeholder groups that -- if you will -- what we have decided are relevant content areas for them and giving us feedback. I believe -- do they have the list of the stakeholders? Well, it's in the Excel guide. I think there's like 20. Isn't there like 20 groups -- something like that? More? Now, there's more. But, there's always more. That's why this has to end so there's never more.

[Laughter.]

Or move to the next phase, as we like to say.

I want to also be clear that the uniqueness of this project is that we are trying to look at newborn screening through the lens of the stakeholders rather than us dictating what they should say. It is that the -- we try to take the view of the stakeholders themselves and do that to the best of

our ability.

Okay. And, so the potential next steps. So, this tool -- once finalized -- once finalized the posted on the HRSA website -- which is the working theory of where it would live -- would then be disseminated to the following.

Newborn Screening Program Listserv -- I don't know if it has an e -- I struggled with that this morning and Google was no help.

Professional organizations -- I've listed a few here, which is, I believe, the strength of our Committee -- our diverse representation of multiple stakeholder groups and our connections to them.

National Conferences, such as the APHL Newborn Screening Symposium webinars and an academic publication, which the goal, I think, of which is not -- is dissemination as well as helping others who might be interested in such a process see how this was done and then perhaps related to newborn screening or related to genetics -- taking this process and then applying it elsewhere.

So, for the Committee members, we would like you to review the document, provide comments back to our workgroup on thoughts about its comprehensiveness, spelling, other issues you might have, and the anticipated Committee approval of the documents would be in the February 2018 or May meeting.

Steps that remain for us are that we need to

continue to complete the vetting of the stakeholders. I would say we have about a third of them done. We then have a process for if the stakeholders disagree, how we resolve the disagreement by consensus of that stakeholder group. And, we've added a few more this past meeting. Once that is done, we would bring it back to the Committee for another final review, having feedback in the interim from you as well.

Do we want to open this to questions now or comments? We have another product. Do you want to go to both?

DR. JOSEPH BOCCHINI: I think if anybody has any questions specifically related to this project, it would be reasonable to raise them now. Jeff?

DR. JEFFREY BROSCO: So, the Taylor reference you had for educational methods was 1949.

DR. BETH TARINI: Yes, it was a good year.

[Laughter.]

DR. JEFFREY BROSCO: It was, but, of course, there have been a lot of advances in how we teach --

DR. BETH TARINI: Correct.

DR. JEFFREY BROSCO: -- and what the evidence suggests is best. So, I wonder how does this guide fit into some of the newer ideas about active learning and how that promotes understanding, skills, and so on.

DR. BETH TARINI: Correct. I should have better explained the limitations of this project and what is beyond

the scope of it in its current form in the workgroup. How one creates educational guides, products, modes of teaching is beyond the scope of this project for this group at this time.

We can, of course, return to that. At this time, this is simply to map out the content areas and to create a systematic way to say, what is it in newborn screening that is important for education, what are those topics, what are those areas, and what specific stakeholders are there, and where does the match and tailoring occur? That is what the design of the curriculum piece is.

What you are talking about --which is incredibly important -- is -- I believe -- how we convey and teach information and educate others. It's the act of doing so. That is not within the scope of this project, but we have discussed it in terms of other members of the working group addressing that issue and/or the working group itself creating or working with other stakeholders such as Baby's First Test and creating best practices based on more current than 1949 knowledge.

So, that's the distinction. This is -- I would call this an encyclopedic type reference -- and, I just made that up, so I don't know if that represents what the workgroup would say -- rather than a how to build and how to educate guide. Does that answer your question? I don't feel like it does based on your -- my nonverbal cue.

DR. JEFFREY BROSCO: It's just I'm trying to picture what this would look like. So, I'm going to --

DR. BETH TARINI: That's why you have the Excel spreadsheet because it is so difficult to picture.

DR. JEFFREY BROSCO: And, I guess my question -- you have thought about this I'm sure already -- is there enough commonality among all those different learners that trying to set up content makes sense? I mean -- if you're trying -- what a genetic counselor needs to know is probably very different from what a nurse midwife needs to know --

DR. BETH TARINI: Correct.

DR. JEFFREY BROSCO: So, is there enough universality in the content that it's worth making it universal as opposed to, here's what we need to know and they need to know?

DR. BETH TARINI: I will tell you from a recent personal anecdote -- although, as researcher, I try to stay away from them generally -- in my interactions with the vetting stakeholders, they are very particular about what they feel they need at the point in time of their interactions in the newborn screening process and what is relevant to others.

So, there seems to be when you look at the Ys and the Ns across that say yes/no in the sort of -- you take the row of the stakeholder and then you see the content across -- there's Ys and Ns if yes applies, no does not. You see a very

varied pattern. So, you see commonalities, and you see diversity. That's what we've seen.

DR. ROBERT OSTRANDER: Bob Ostrander with the American Academy of Family Physicians. First, a request -- where you have pediatricians and providers, would you mind throwing family physicians in there, because we really hate being called providers.

DR. BETH TARINI: You and Cathy DeAngeles share that feeling.

DR. ROBERT OSTRANDER: Yeah. I mean -- physician has become my go-to word because everybody else -- you know -- we've now got --

DR. BETH TARINI: What if I said clinicians?

DR. ROBERT OSTRANDER: That's fine. I guess -- I guess I'm putting my Academy hat on as much as anything, and I know if I acquiesce to something that specifies pediatricians, it kind of --

DR. BETH TARINI: That's fair. I agree.

DR. ROBERT OSTRANDER: Because if I'm ask by specialty, my bosses are going to be made at me.

DR. BETH TARINI: Fair.

DR. ROBERT OSTRANDER: My second question is -- and, maybe you went over this and I missed it -- but, how -- who decided where there was a Y and where there was an N? I mean -- did you -- I mean -- it looks like a lot of stakeholders

they've actually talked to and found out what they thought their needs were.

DR. BETH TARINI: So, first the Committee sent one of their representatives from -- I would say probably in that room -- greater than 50% of the stakeholders are represented. So, the Committee went through -- the workgroup -- I'm sorry -- went through and did its preliminary assessment, and then each stakeholder group -- we've called stakeholders -- and they have now gone through -- they are going through -- so, it's in process -- and they are vetting the Ys and the Ns. Does that answer your question? Okay.

DR. ROBERT OSTRANDER: Okay. Thank you.

DR. BETH TARINI: Okay. Amy's going to present the next project, and then I'll come back.

MS. AMY GAVIGLIO: Okay, so the second project we're going to be discussing is the Abnormal Newborn Screening Result Communication Guide. So, just as some background -- especially for the new Committee members -- the need for this really arose from work done by Natasha Bonhomme and Dr. Carol Greene that used focus groups of parents who had received abnormal results and really talking about what that initial notification process was like as well as, of course, I think all of us within Newborn Screening Programs have heard anecdotal evidence -- sorry, Beth, that we're going to use anecdotal evidence -- from families on what that initial notification was like for them.

So, the purpose of this document is to provide guidance to primary care providers in helping frame the initial discussion with parents about abnormal newborn screening results. I want to talk a little bit about the scope of this because this really is not to provide them the clinical information -- the analyte-specific or disorder-specific information that is well covered by ACMG Act Sheets or state-specific Act Sheets, but really to provide guidance on points of discussion -- what I would kind of consider the touchy-feely part of having this conversation.

So, the models that we used -- the first one is known as the SPIKES model for delivering high-anxiety news. That particular model is rooted in the oncology literature as well as, of course, pulling quite a bit from the genetic counseling literature. You'll notice you do have a copy of the Communication Guide in paper in front of you. So, we actually modified SPIKES to be called SCREEN for this purpose. So, the S is to share the specific positive newborn screening result with the family. The C is to assess the family's comprehension of newborn screening. The R is to reiterate what screening is and is not. E is to engage the family with knowledge and information. The second E is to address the family's emotions around this newborn screening result. And, the N is to give the family next steps and resources.

So, the goal of this is -- and, this was a difficult

goal for us to reach because as we started writing through this, we wanted to add as many examples as possible and make it as comprehensive as possible but really to get down to a one-page document, so balancing all of the guidance we wanted to give with ensuring that it was actually a practical document.

The review process thus far has been certainly Baby's First Test staff. Natasha and Amelia have been fantastic on providing guidance with this, especially coming out of their initial research, which led to this project. We have had primary care providers look at it, genetic counselors. I believe, Dr. Brosco, at the last meeting -- you had mentioned the need to have a communication expert look at this. Cathy Wicklund did pull someone from Northwestern, and she has looked at it, and her feedback has been incorporated as well as at this point, all of the Education and Training Workgroup members.

So, next steps, now that we have created the document and feel pretty good about the content -- what are we going to actually do with it. Our potential dissemination strategy is to provide the content to states for inclusion potentially with their abnormal result notification package. So, typically when there is an abnormal result, the report as well as some fact sheets get sent to the primary care provider. This is something that could be ancillary included with that.

You will notice that the guide you got is just a

word document -- black and white. That is so we can just focus on the content at this point. We, of course, will take the time to prettify it -- is that a word -- to make it look more user friendly.

A second potential dissemination strategy -- and, we've talked with ACMG about this -- is to provide the content for inclusion as part of the Act Sheet process. So, this would kind of be considered a pre-Act Sheet. Certainly providing content on newborn screening education sites like Baby's First Test. We talked about potentially StarG, newbornscreeningeducation.org, I believe.

And, then the other thing to consider -- you know -- in terms of really getting this into the hands of the people we want using it is developing a potential AAP Maintenance of Certification course module and/or obtaining endorsement by the AAP.

For Committee members, the next steps are very similar to what -- what Beth requested of the previous project. We would ask you to review the document in the interim between the meetings and provide comments back to us -- again, really focusing on content, not so much on formatting. And, we are hoping for Committee approval of the document content at the February meeting.

And, I think with that, I will turn it back over to Beth -- who looks confused -- to come back.

DR. JOSEPH BOCCHINI: Okay, thank you.

MS. AMY GAVIGLIO: Oh, you have questions? Yeah.

DR. JOSEPH BOCCHINI: We'll just take a few questions. Let's see if there are any questions or comments. I have Jeff and then Scott. Joan? Okay.

MS. JOAN SCOTT: Just a real quick question because I see you're using the term a positive newborn screen, and I know there's been a lot of language -- you know -- discussion back and forth about positive and negative, and the value as opposed to saying something like out of range, which doesn't mean is it normal or abnormal. So, I see smiles -- you've discussed this?

MS. AMY GAVIGLIO: We did. Yeah. We originally had out of range in there, and then we learned that some states use out of range to mean something different than what we would think of out of range. It's not analogous to a positive or abnormal screen. So, our thought process on this is that -- you know -- we'll probably put it in brackets, and it would be -- you know -- choose your own adventure based on how you -- how you provide that information. You know -- if you're using the word positive on your reports, then you should use the word positive here. If you're using abnormal, use abnormal out of range. So, that would be something that would be customizable to the state.

DR. BETH TARINI: And, to add to that, this document

does not have to be used -- right? It does not have to be used as it is for the programs, for instance. If you put that bracket, that segues into the discussions we've had that you can take this and say, oh, we use this word, and we would like to have that word in it, and so they can customize it as they wish. Sorry, Beth Tarini.

DR. JOSEPH BOCCHINI: We've got Jeff and then Scott.

DR. JEFFREY BROSCO: Did you -- I didn't see in your list -- did you have a chance to sort of try this out with like an informal focus group and sit with a couple of residents or clinicians and say, is this helpful?

MS. AMY GAVIGLIO: No, not yet. But, we certainly have talked about actually evaluating it in that way to see if they found it helpful -- if they felt like the conversation -- they were more comfortable having the conversation.

DR. JEFFREY BROSCO: Just informally might be nice. And, one of the things I found in doing this, they often -- students -- they sometimes like it when you even suggest language like exact words, like "This is what you might say to a family." And, that level of specificity gets beyond the abstract -- you know -- share emotions with family to, "How are you feeling now?"

MS. AMY GAVIGLIO: So, you're saying provide actual examples within?

DR. JEFFREY BROSCO: You might get that feedback.

MS. AMY GAVIGLIO: Okay, thank you.

DR. BETH TARINI: I -- this raises an important question that I have for the group. The Education and Training Committee struggles with a number of challenges. One, it's scope is vast. Its leverage in the vast scope of education is small, and its resources are vanishingly smaller. Therefore, I'm seeking committee guidance on how much -- at some point there's a level of validity testing, and at some point -- like it seems to work -- it works in the real world -- and, that we've done a due diligence of upwards of an RO3 or manuscript publication.

And, without resources and with limited time of the members, it is difficult for me to understand where Cathy and I need to draw the line on this because we don't have the resources or the bandwidth to do extensive testing. Although, I agree that simply throwing something out that's not been to some degree tested, if you will. The question I have is where is the line between enough and none. So, any feedback from the Committee or guidance would be welcome.

DR. KAMILA MISTRY: Sure. I think it's a simple answer -- but I think it depends on how it's being applied, and in terms of -- you know -- balancing are there any harms, are there any -- you know -- trying to think about it more broadly, and also in terms of -- you know -- including it in MOC and things like that. I mean -- what's their bar in terms of the

evidence or -- you know -- it being cognitive -- you know -- tested in terms of cognitive testing or -- you know -- evaluated in some way. I don't know.

MS. AMY GAVIGLIO: No, I think that's a good place to start.

DR. KAMILA MISTRY: There needs to be some transparency around what happened -- how is it evaluated, how is it -- and this is Kamila -- and -- you know -- I think that's also very, very important just so that's clear.

MS. AMY GAVIGLIO: Correct.

DR. BETH TARINI: I think -- this is Beth Tarini -- I think -- I think perhaps a starting point then might be to say, what are the potentialities that we need to at least look at. I mean -- I would say to push back -- we mandate disorders that must be done and have minimal review based on minimal evidence of the harms. So, to have that grade for an educational handout seems out of scope or out of balance. But, I think we could certainly have the discussion about what are the pros and cons and the harms and the benefits.

DR. KAMILA MISTRY: One quick followup, which is just that -- you know -- in terms of cognitive testing, that might be something simple, but I think it's important to make sure from a validity perspective that what you have here is being interpreted in that way. It's something simple, but I think it offers some evidence at kind of a low -- you know -- I

don’t think it’s a big cost to do that, but I think across different stakeholders and things like that -- I think offering that up and having that sort of in your pocket will be an important step.

DR. BETH TARINI: Which workgroup are you on?

[Laughter.]

DR. JOSEPH BOCCHINI: All right. We’ve got Scott, Mei, and Sue.

DR. SCOTT SHONE: So, Scott Shone. So, I appreciate you talking about in terms of next steps potential dissemination strategies, but my comment, I think, circles around what was just being discussed, which I don’t think the goal should be dissemination but actually use. And, because there is a clear -- and Beth just said it -- there’s a lot of time and effort that’s being poured into this -- these ideas. But, if they’re simply just disseminated to whether it’s -- you just talked about, Amy, in terms of pediatricians or family physicians -- so that Bob doesn’t have to raise his hand and add on to my comment -- clinicians or in terms of the spreadsheet that I just went through -- you know -- genetic counselors and things like that. And, so I’m wondering if there’s an opportunity here to have commitments from the groups who are not only contributing to these documents in terms of content but contributing to figuring out ways to have their members of their organizations use them -- genetic counselors,

pediatricians, family physicians. Because, otherwise, there's a lot of time going into this, and it's just another document that a workgroup of this Committee has created, and I know that that's the ultimate goal, but I think that with limited resources that Beth just identified, perhaps getting that initial agreement to help use the documents would help guide where the scope because if people aren't going to agree to support its use, then that might tell you how much effort to put into creating it.

DR. BETH TARINI: This is Beth Tarini. So, if I'm understanding you correctly, simply sending it to the AAP and saying, here you go, versus having them endorse it -- is that the type of --

DR. SCOTT SHONE: I don't think it's endorsement. But, I think that them actually saying to their members, here is something that is coming from this Committee that we've contributed to -- you know -- there's a different -- I think there's a weight to endorsement. But, there's also a support for its use -- you know -- that could still hold water in terms of -- you know -- putting meaning to your substantial efforts.

And, I think that goes -- I actually think that goes across the board. We talked a little about timeliness yesterday, and I'm not going to -- I'll have comments when Kellie talks about a similar thought is that there's a lot of groups here that are throughout the system, and it's not just

the Education Workgroup or the Lab Workgroup who are shouldering the burdens -- but everybody who's sitting at the table.

DR. JOSEPH BOCCHINI: Mei?

DR. MEI WANG BAKER: From the discussion, I think Susan is saying that I cannot understand better because my original question -- one question is this document is for general education purpose or because you mentioned some in the package you send a report so this is what I want to make a couple of comments. I think the most important fact -- I use primary care providers because I need to think about midwives too.

So, I would think the most important message is the risk assessment if newborn screening is the key. So, I think like all the residents and medical students through my laboratory, if they are left with this concept, I think it's a success. The reasoning is with this in your mind, you communicate with families in a different way. We only say newborn screening because we're trying to set a threshold that's more conservative and that if you are in this group, you have a high risk. In other groups, you have less in comparison. So, I think because I often hear it said that newborn screening is right, newborn screening is wrong. It's not. So, I think it's important the elements I would like to see this happen. And, another thing is when you talk about

communication, I think, don't forget we have our specialties in that. So, for our program, you have a consultant. Actually, you need to communicate with them how much what you need to say to a primary care physician, because they will immediately come in and you don't want the message to get so confused. So, I think that's the part I want to mention that.

And, the third part is in terms of [inaudible] with the report. My understanding, actually, I think most of the program doing such and such is abnormal -- I use abnormal -- abnormal normal newborn screening -- actually you call the physician first. They don't see the resident there because they're never different. And, I was impressed by one clinician. I would call her on the Pompe result. She asked me, what is your positive predictive value?

You know -- all these things -- I was very impressed, actually for these questions. I think these are things that we need to kind of take into consideration.

MS. AMY GAVIGLIO: No, I think that's -- all three were really great points. And, I'll start with your second one, I think, in terms of specialty care. I think certainly if that's -- you know -- we know each state has different communication models when it comes to out of range/abnormal/positive results. So, if that's a model that you use, I think that certainly could be something provided to your subspecialist as well as your primary care providers.

In terms of risk assessment and things like positive predictive value, I know that those are very important things and things that we need to get across to families, but not -- I would say -- I know the idea of genetic and health literacy came up and risk assessment is not always very well understood. So, I think providing numbers doesn't always work, and sometimes you have to provide more qualitative information.

So, one thing we talk about -- you'll notice in the first bullet -- where it says the newborn screening result is serious, but that you will discuss the next steps together. And, we had -- you know -- the conversation of well, maybe not all newborn screening results are serious -- the positive ones -- if we think it is likely a false positive. But, for the family, it's serious, and it's a balance of not saying -- you know -- that you have low risk to a point where that family doesn't want to follow up versus scaring them too much. And, so trying to find that balance and communicating the risk was something we talked quite a bit about with this project.

DR. MEI BAKER: I just want to quickly say -- this is Mei Baker -- I didn't.

DR. JOSEPH BOCCHINI: Okay. Sue?

DR. SUSAN BERRY: Sue Berry. See, I remembered. So, a couple things. I think this is a great step towards avoiding the doctor that calls the family or the provider calling families saying, don't worry about this, this is

probably nothing. Because we kind of don't want to tell people that, and it's a very common response. Two practical suggestions. Why don't we use some of the tools we have available to us like the network of -- I don't know what they call them now -- they used to call them the collaboratives, but now the genetics networks that are HRSA funded -- our own Midwest Genetics Network has a Provider Education Workgroup. If you want a vetting process, it would be really easy to invoke that -- ask that group of providers to give you some feedback. So, that could be a quick and easy, and, I think, very useful. So, I'm going to make that offer.

MS. AMY GAVIGLIO: Thank you. That's a great idea.

DR. SUSAN BERRY: Because we can do that.

MS. AMY GAVIGLIO: Perfect. Thank you.

DR. SUSAN BERRY: I already got my okay from Cindy. She said it was all right. And, the other thing I would say about working with organizations -- for example -- the American Academy of Pediatrics has a Council on Genetics. We can certainly turn to them. I know that we can speak to them because I have to go to that meeting in a couple weeks, and if there are things that we need organizations to do, you turn to -- I think -- the appropriate -- at least in some places there are subspecialty groups that can help support the activities that you want to do.

So, it's not the job of this -- of your workgroup to

take that on. I think it's more the job to pass it on and have other people support you.

DR. BETH TARINI: No, I totally -- I completely agree -- this is Beth Tarini -- I completely agree. I did not mean to say that each one in the workgroup needs to vet it, but organizing and implementing and reviewing the vetting is no small task. So, that -- and, as a member of the COG -- the Committee on -- former member of the Committee on Genetics -- I think they would be an excellent place.

Some organizations tend so to be a little touchy about what they -- the AAP at times is -- has its hesitancy about what it will endorse. I don't think endorsement in and of itself is a goal. It's what endorsement may get you, to Scott's point, as the ultimate goal or the outcome, which is usability or uptake in usability among the members.

DR. SUSAN BERRY: Yeah, in that context, I wasn't offering endorsement because that's not mine to give. But, it's another group of great professionals that could provide feedback.

DR. JOSEPH BOCCHINI: I've got Scott. So, I've been reminded we have two Scotts. So, I have Scott G and I've got Carol.

DR. SCOTT GROSSE: This is the Scott corner today. I think usability testing is very important for any open facing material such as this. And, so, I was going to ask the

question, which was partially answered, is whether within the HRSA-funded network of collaborators or system resources for usability testing. There may be others.

DR. JOSEPH BOCCHINI: It certainly is a possibility. Carol?

DR. CAROL GREENE: So, first I want to say thank you. This is fabulous. It's all on one page, and it for the most part -- you know -- I have three specific comments. But, I think it really fits with the focus groups that were done that we heard from the families.

One comment is, I wonder if there could be a companion sheet with some suggestions of language because it sounds like there was a lot of discussion about -- you know -- fun easy ways to explain what a screen is and risk, and -- you know -- putting in some language. So, maybe a companion sheet that -- don't change that it's one page.

And, then two specific comments. One is -- and I will give comment. But, we have starting with the share the specific results, and that goes immediately to understand what is screening, which is great and important, but it doesn't say way at the top -- it's not until halfway -- two-thirds of the way down the page that you say, what's the disease. So, remind people to say -- because, remember -- these are people who are calling in saying, your PKU was positive for biotinidase.

So, I think way --

MS. AMY GAVIGLIO: Right. That's a great point.

DR. CAROL GREENE: So, I think way up at the top in the beginning, it has to be -- you know -- share the specific positive newborn screen results. By the way, that means name the disease.

And, then starting with the engage the family with knowledge and information, and then farther down, provide valid websites. That does lose track. And, it's the one thing that got lost, I think, here in the focus groups we had is some people said, what I had was too much information. I learned all about the disease. I only wanted to know where I go for my lab test.

So, I will provide specific comments, but it's not engage the family with knowledge and information, it's engage with the family and explore what do they want. Do they want information about the disease, or do they just want to know where to go for the blood test and what to watch for.

MS. AMY GAVIGLIO: Yeah. And, we try to address -- that point came up. Natasha certainly brought that up several times, and we tried to address that in bullet 2, where we say at the family's pace and desired level of detail, but --

DR. CAROL GREENE: But, that's not a sub-bullet. That's --

MS. AMY GAVIGLIO: Okay. I see what you're saying.

DR. CAROL GREENE: -- providing people with engaging

with information. And, I agree with Natasha. We were both at that focus group. We heard it -- we heard it. It's engage with the family, not engage the family with the information -- it's engage with the family and then figure out what they need, and then do it together.

MS. AMY GAVIGLIO: Okay.

DR. CAROL GREENE: And, that I really -- I will provide some comments. But, I really feel strongly. We heard from the families that that's -- this is starting to read like a doc that is providing information as opposed to a partnership.

MS. AMY GAVIGLIO: I look forward to your specific feedback, absolutely. Thank you.

DR. JOSEPH BOCCHINI: All right. Additional comments or questions? If not, Beth, you can continue. Thank you, Amy.

DR. BETH TARINI: So, now I'm going to talk about some future project ideas. But, on the heels of that discussion, I'm wondering if perhaps we take some of these projects and then move them into a phase 2. And, then I would ask the Committee for their input as I present these projects to not only discuss and think about the relative importance of the issues that we're going to present that we've discussed about future areas to address and input on strategies about these areas, but also whether the Committee feels at this

point, given the feedback, that we should create phase 2s of what we have done thus far and then dig much deeper because we've actually not sort of discussed it. We have sort of, I would say -- I'm speaking for the workgroup members -- we have in our meetings thought of these as one year or less projects -- sort of, here you go, find a project, make it happen, let's do it. And, it may be in our group that that is just not something that is effective or that with a bit more time, we can do a little bit more.

And, so, in fact, taking a whole 'nother area and superficially addressing it is not where the value lies -- going much deeper in one area maybe. So, I just put that out there because that's not, I would say, how the discussion in the groups has been historically, even going back in my last reiteration as Co-Chair around these projects. So, that just -- I'm going to put that out there.

So, some issues we discussed -- problems, if you will -- challenges in the areas of education and training were designing intervention strategies for optional newborn screening. The example and issue that came up was that in Ohio, there is optional Krabbe screening, and there is a significant -- I don't have the exact number -- proportion of families that are opting out of this screening, and there is concern that their opting out may not be based on informed decision-making. And, the Newborn Screening Program and

Committees in Ohio are dealing with this now, and one idea is as part of their work, can we help them with their process. There is a slight snag as of recently as how that project might be implemented from a regulatory standpoint, but that is one potential option that has been discussed at this meeting and at the last meeting of the workgroup.

The other is address and determine educational needs for newborn screening conditions with adult-onset variants. This has become a prominent discussion point for the Committee during the recent nomination discussions. And, so the question is, what are the educational needs that we need to be thinking about as we provide newborn screening results that may have implications for adult-onset symptoms.

The final is -- was brought up yesterday and touched upon -- carrier status, especially as it relates to improving educational outreach around hemoglobinopathy carrier status. This is a broad topic -- outreach understanding, misunderstanding, etc.

So, I would say that each of these -- given our recent discussions -- are quite broad topics. I could try to write an RO1 for an HOBI on the last one. So, I am hesitant based on the last discussion to delve into each of these without Committee guidance on where they think our time and resources would be best spent for impact on the community. So, I open it up for discussion.

DR. JOSEPH BOCCHINI: Annamarie? Scott S?

MS. ANNAMARIE SAARINEN: Thank you and Amy both for these presentations and your work. As a parent, I'm sort of overjoyed.

DR. BETH TARINI: I'm glad someone's happy.

MS. ANNAMARIE SAARINEN: I am. I'm overjoyed. I'm beyond happy to see this communication and how we can open up the channels and make this a better experience in the worst of possible circumstances for families. So, I think it's awesome.

So, I have two questions, and I vetted my first one with Kellie so I didn't feel like a complete idiot. But, the optional NBS -- is this something that's happening in many states, and is it specific to Krabbe, because this is new -- I've not heard of how often this is happening where it's not part of the traditional opt out.

DR. BETH TARINI: I didn't know if anyone -- otherwise I'll call Aaron Goldenberg. Do you want to come up? You've been vetted -- you spoke yesterday.

DR. AARON GOLDENBERG: So, in Ohio, it's not -- optional is an interesting word because it's on the panel -- it's not -- it's not a -- it's not an extra condition. It's on the panel. It's on -- it's meant to be mandatory. But, because it wasn't added to the RUSP, the state decided to add a separate opt out option. So, when parents get the brochure for newborn screening, they get the regular brochure, and they get

a one-pager that talks about Krabbe, and then they have the option to separately opt out of -- of just Krabbe screening. They can get the rest of the panel, and they can separately opt out to Krabbe.

But, what's happening is that they're seeing -- you know -- in a 6-month period when you may have maybe 10 or so opt outs for the entire panel, they are seeing over 3,000 -- 3 or 4,000 opt outs for Krabbe. Unclear what's actually happening with that. About 160,000, I think -- maybe 130 -- I can't remember.

So, many of those opt outs are coming from zip codes that have high Amish populations in Ohio, which is -- and, so there's some -- some knowledge at the state level in talking with the Amish community about Krabbe and about screening. And, it may be that these opt outs are very meaningful, right? So, that's the question that I think is important for the Committee to think about. Maybe these are actually really meaningful and actually okay opt outs. But, the state has mandated screening for Krabbe, and so there's this interesting educational question that I think we've been talking about, which is how do you educate about a condition that the state has decided we want to screen, but has this very interesting option. And, I think Georgia has also been dealing with this, right, but has gone more of an opt-in, I believe, approach.

And, so I do think there's an interesting set of

educational questions for the Committee -- for the workgroup, which is as conditions that have slightly different opt-out procedures or slightly different opt-in procedures, what are the potential educational needs, and how do you communicate that with families.

MS. ANNAMARIE SAARINEN: Okay. Thank you very much. So, yeah -- you might want to stay.

Now, this raises something really interesting. One is whether or not this was a unique scenario to Ohio or condition-specific scenario, or if that was like, oh, since Krabbe has been added, there are several other states that are doing it, but since you mentioned Georgia and the variables around opt in versus opt out. I don't know if maybe NewSTEPs or someone else has -- either has or the ability to define for the Committee how many states are dealing with what we would consider nontraditional, right? The thing that all of us thing of as the normal opt-out formula for screening. And, if it is more than several, I think this is probably a very good target for your workgroup.

DR. BETH TARINI: Oh, see, I was going to actually say that that seems beyond the sort of scope because if we are going to say what the states are doing and -- I'm not saying that this issue isn't important -- but, I would say perhaps this needs to go back to the Committee about programmatic organization, and how they decide what they put on the panel,

what they don't, and what's optional. And, that discussion, I think, perhaps may be best in the Committee and outside of the E&T.

MS. ANNAMARIE SAARINEN: Yeah. And, I hear you, and I think you might be right about that. But, I think just gathering the information might be the first step.

DR. BETH TARINI: Oh, certainly. HRSA can do that.

MS. ANNAMARIE SAARINEN: If we could come back and see -- again, to find out whether this is sort of like symptomatic or if it's pervasive, or where it's at, because I think at that point, we start having pretty substantive discussions on that, and I feel like Baby's First Test has done a lot of this too. Where should the engagement really be happening -- or the educational education really be happening. And, in my mind, when you have something like what this example is, it's got to be happening before the birth setting. I mean -- no question.

DR. BETH TARINI: I agree. I think -- I think getting an understanding and a handle on the landscape might be a first step. Is Jelilly in the room? I don't mean to throw him under the bus. He's in the back. But, since NewSTEPs has as it's purview the information on each of the states and what is on their -- Marcy's nodding, so good -- write that down -- Marcy was nodding.

[Laughter.]

So, that may be a place to start since they one, house the information, and two, can get a better sense of where it is. And, then we are happy then to revisit this at a later time and add it as an adjunct project about specific educational opportunities that might exist.

MS. ANNAMARIE SAARINEN: I think that's great. Thank you for your responses, and I will just say from the Newborn Foundation's perspectives since we're -- I know this is Committee crossover as we're a group crossover -- but, since -- since this policy piece around newborn screening is sort of really a part of our DNA, we're really, really committed to making sure this doesn't become a problem. And, I think of how this interesting nuance for Ohio -- and I don't if they've looked at that data -- but, if your given the opportunity to opt out for Krabbe as a separate thing, is it impacting the rates of opt out for the overall newborn screening panel? And, I think that would be a very interesting thing to look at.

DR. AARON GOLDENBERG: Right, and we've talked a lot about that. And, I actually think -- this is totally my own -- this is not based on any data -- I actually think it's actually lowering the rate of opt outs because the way that the brochure is worded -- the one-page brochure is worded -- makes it seem like this is the one you can opt out for, the rest are mandatory. That's only my opinion from looking at the materials. But, we've been wanting to do a study in Ohio and

the state program and the IRB is all on board, and we're hitting a legal hiccup that is not allowing us to move forward. But, the idea would be to do interviews and surveys with everyone who has been opting out. And, everyone's been excited about the project, and I think it will eventually go forward.

But, I do think this is a really important point in time to think about the connections between opting out, permission, consent, and education where these kind of unique -- even if they're one offs -- these unique one offs allow us to rethink some of those issues in ways we haven't before, and what it means for expanding panels, those kinds of things. So, I appreciate the comment.

DR. BETH TARINI: And, we did do a study -- I don't have it off the top of the head -- at the University of Michigan where we did hypotheticals as in we presented the participants of the survey with information on Duchenne's with Brian Zikmund-Fisher, and I believe that was published, and whether or not having an optional, affects what you want if you were given a mandatory panel. I can look to that data and that paper and send it to the Committee. It was hypothetical, but it was --

DR. SCOTT SHONE: All right. Scott Shone. I'll try to keep it quick because I know we're up against time here. So, just back to the original question you asked Beth about do we stick with the current projects or go something like this.

You know -- my personal preference is to try to take what you're working on and have it come to a complete and meaningful conclusion as opposed to -- while a lot of work -- a superficial pass of a topic, despite how critical these three topics are. So, that's my comment is I think that the phase 2 -- I think that's actually a common theme across the workgroups we'll hear today is that there's been a lot of great work done, but there's more to do, and what's great is their ideas of how to continue it and make it more meaningful. So, that's what I would say with respect to this optional topic.

DR. BETH TARINI: So, I think that that's something I would like to just pause you -- I would like then the Committee to talk about this because that has not been -- and, I'm not saying this is good or bad -- that has not been the sort of thought I have felt either way -- the guidance from how the workgroups should be addressing their projects. And, if that's -- I don't think it's actually ever been discussed explicitly. So, what has been -- you know -- internalized as do your projects there year-long. So, that would be helpful for the Committee to have as a whole like, what do we want the workgroups to bring to the Committee, and what is their ultimate achievement we're looking for. So, thank you.

DR. SCOTT SHONE: Okay. And, with respect to the optional screening -- this is an issue that's beyond E&T. It's -- everybody's going to have to deal with this. And, I think

that I don't agree with the term problem. It's actually an interesting challenge and an opportunity for parents to really figure out what is newborn screening, where are we going, and what are my options in the field. And, I think -- you know -- there are great possibilities for additional optional panels, where they're not RUSP conditions -- you know. They've gone through -- either they've gone through the vigorous evidence review and don't meet the criteria or they haven't, but a state decides to do it in this manner where a parent has the -- their right -- you know. You mentioned mandated, Aaron, and that's what it amounts to in most states is that the state has decided it's the benefit of the child, and the parents' right is they might have an opportunity to opt out, but the government has decided this is so important to the public's health, that we're doing this. And, some of these conditions don't necessarily meet that bar, but the parent might want that information.

And, I think that we, as a system, need to think about that -- not just education, not just lab, not just followup -- but everybody. So, I do agree with you, Beth. It's Committee, and the Committee needs to think about if we want to attack this, how to cross cut all the workgroups to attack the -- to approach the issue.

Dr. AARON GOLDENBERG: Yeah, I would just add -- so, I absolutely agree with you, and I would add that while my voice may be somewhat of a minority voice in Ohio, when I see

the large numbers of opt outs, my automatic response is, well, that's terrible. They shouldn't be opting out. There may be actually very rational and good reasons why people are choosing to not have the screening -- I don't know. That's why I want to do this work. And, maybe a lot more interesting and actually challenge is a good word, but actually more meaningful than just saying, well, I don't want the government to have my DNA, so I'm going to say no. And, actually, when we think about the condition and how it's been rolled out, I think it's important for us to understand how parents are making that decision, and that's really important. So, I really appreciate the comment.

DR. BETH TARINI: I also think that if we disagree -- if we think the parents are making a bad decision, then it needs to be mandated. There is no -- either they're allowed the choice and have an informed choice, or they're not allowed the choice. And, once that decision is made, you have then decided it's mandatory.

DR. MEI WANG BAKER: Yeah, it seems we are talking about -- this is Mei Baker. It seems we're talking about the opt out, I just want to add in a little bit of information from our experience. So, from the description you have for the opt out for Krappe, it sounds like exactly what we are doing for Pompe in Wisconsin. The rational used is adult-onset. In terms of general newborn screening, we -- our states uses opt

out. Anybody can opt out without question. And, we don't have people opt out. That is something we know that. But, for Pompe, we made extra steps. So, we have the material on the website, and we disseminated the one page to like ACOG and AAP, and we have it set up with a 1-800 number. We have a website. I can tell you we started middle of July up to now, we have two of that, and it's through the phone.

So, we do ask for a callback number, so they do leave the callback number, and I kind of want to find out like why you opt out, but I don't want to push. So, I always call back to them, give them my phone number, and neither one called me back. So, I think it's a very interesting -- the one thing is when you talk about opt out -- meaningful opt out is we don't really know how the information has been reaching everybody -- so, we don't know. But, we've been asked by our state when we do this pilot, as far as we put a serious effort -- that's how far they want us to go. That's how far we did, so.

DR. BETH TARINI: Right. I don't think that -- this is Beth Tarini -- I don't think we've had a discussion. And, I'm not sure -- I don't think it's in the E&T -- I think it's in the Committee discussion -- what is an informed decision. I mean -- the people that make decision aids have trouble sort of actually with the definition of informed, and agreeing with me is not the definition of an informed decision. Me agreeing

with you is not the definition of an informed decision. I'm not saying you're saying that. But, the philosophical struggle is, when have we done our due diligence in 1) making sure we've educated, and b) making sure -- at the very least a and b) -- and b) making sure that the person has received it, understands it, and has made a choice.

There are studies that show that people can get 100% on an HPV vaccination knowledge screen or knowledge test for their child and not want the HPV screen -- the HPV vaccine, sorry. So, that is -- we just have to -- I think -- if we weigh into this is decide what is going to be our outcome, and are we comfortable with our outcome of the education around optional for opt out.

DR. JEFFREY BROSCO: So, I agree that all three of these are wonderful topics, but I really like the educational primary care and the things that you are already doing, so I would recommend sticking with that and getting to a place where you think it's ready to go.

DR. BETH TARINI: Perfect.

DR. DIETRICH MATERN: Yeah, about the opt out, I don't think that we should spend a lot of time in worrying about the optional tests as in Ohio for Krabbe. If it's not on the RUSP, the extra conditions -- I don't think we should worry too much what the states are doing.

The similar situation is, I believe, in Pennsylvania

where some of the RUSP conditions are, I believe, mandated, but you can still have -- if you want to -- the additional lysosomal disorders. I don't know if Cate or Kurt can comment on that -- how that is going. But, again, I think overall consenting and all these things are important for us, and we should keep track of what's going on, but I don't think we should spend a lot of time on it.

DR. JOSEPH BOCCHINI: Natasha?

MS. NATASHA BONHOMME: Hi. Natasha Bonhomme, Genetic Alliance. I have to politely disagree with that because when we then talk about we need to educate about newborn screening, what people are getting is all of newborn screening and whatever is at their state level. And, so depending -- I mean -- maybe go back to the charter of this Committee -- is it just about RUSP or is it about newborn screening in this country?

And, I bring that up because this is where this conversation is happening nationally. And, so we really need to know not just what our state programs is hearing back, but what are the questions that are coming up from parents, from families, that may be funneled into a number of different places. I bring up we have asked the experts on Baby's First Test, and the types of questions we get -- it's very clear that people don't know to go to their states, and they're not interested in going to their state program. They just want to

type it in and get an answer and go on to their next piece of their life.

So, I think this push to really think about this as a system and not just, what should this workgroup do, what should that workgroup do -- but, what are the actual questions this Committee should be looking at. We need to be reflective of the reality of newborn screening on the family's side, on the public health side, and along all the different components of newborn screening. So, I'll leave it at that.

DR. JOSEPH BOCCHINI: Thank you. Dieter?

DR. DIETRICH MATERN: Sorry, can you -- but, what are the questions that they actually have when it comes to optional testing? What do we need to fix or educate people about here?

MS. NATASHA BONHOMME: Did I not state my name before? Just a reminder -- this is Natasha Bonhomme. I mean -- I think we can go through -- and, that's like a whole project to assess -- like, what are all the different questions coming up. But, I think -- and, I guess that is the question -- I guess it's a philosophical one. Is it that you wait until people have questions, and then you try to fix it, or is it as a system is going in a particular direction, you try to think based off of history and what has come up to see what are the things that we can do if states are going in these different directions to actually be there for families, for providers, as

it's being built as opposed to let's wait and see what happens. Again, that's a philosophical piece, and I can't say that. It's not my job to determine that for this Committee. It is my role, I think, to speak for the families that we do hear from.

DR. JOSEPH BOCCHINI: Is there -- no? Okay. I think we've had a really good discussion about this, and I think from the comments is that the consensus of the Committee that the E&T Workgroup should continue to work in greater detail related to these two projects to make sure that the efforts that they've put in result in something that is usable, acceptable, and potentially tested for effectiveness before going on to other projects, while we still can keep these on the table as potential things that either the workgroup or the Committee may need to address, but, do it in this fashion so that we give some direction. I'm here seeing lots of nods yes. Okay. All right. You have your directions. Thank you.

DR. BETH TARINI: Thank you.

DR. JOSEPH BOCCHINI: The next report is from the Followup and Treatment Workgroup, and Jeff Brosco, Chair of this workgroup will make this presentation. Jeff?

DR. JEFFREY BROSCO: Thank you. So, first I would like to thank the workgroup members. We again yesterday had a very energetic and enthusiastic conversation. It's clear that people really are invested in this issue, and it's wonderful to be a part of it. I also want to thank Catherine Camp, Joanna

Monaco, and Alan Zuckerman -- all of whom are ending their formal service on this workgroup, but we have lots of folks with informal work, and I hope that they continue to attend and participate. We don't have any new members yet, but we should point out that Sue Berry, who has been a workgroup member forever, is now a Committee member as well.

So, basically, we have four things to talk about. The environment scan and how we hope to work together with Alex and K.K. and their group. Secondly, this idea of creating a -- a road map to what the future of a long-term followup system might look like. And, I just put in there for a minute that the L-word can mean different things. We've always talked about long-term. Yesterday, we were chatting about whether longitudinal might be better or even lifespan, and before everyone at HRSA freaks out -- when we talk about this, what we mean is that when we're taking care of a 2-year-old, we think to think about what that might mean for that child when he or she is 50. And, so knowing the longer-term outcomes is -- we think -- part of our purview. We're not talking about taking care of 50-year-olds now.

We do want to follow up with the medical foods report and the Quality Measures report. So, to go through each of these quickly. I'm going to do the last two first, because you have heard from me often already about these in two of our current sub-workgroups. This is activities 3 and 4 in the

previous slide.

So, the first thing is the medical foods for inborn errors of metabolism. Sue Berry has been leading us through this. The report is basically completed. The last Ts are being crossed and Is being dotted. And, the last remaining issue really is about what kind of publication came out of this. We would like to see it widely disseminated, and although our website gets lots of hits, we want to see if we can go beyond that in the peer-reviewed literature. So, we need to think about that over the next couple of months, and Sue will continue to take the lead on that.

Secondly, the Quality Measures. You've been hearing about this in the last few meetings. Alan has been leading this. We've had lots of help from Carol and Kamila and Margie, and really the entire group. I think almost every single person has written at least a paragraph in this report. It's now 26 pages plus about 20 more pages of appendices. And, we have almost -- I think -- all the pieces together. We just need to make sure they're all there. And, we want to spend a little bit of time working on the executive summary in particular so that we have a very crisp just 1-page description of what it is we found. And, I do think there's a little bit more work we need to do on the specific recommendations. So, we would like this to be something we continue to work on over the next couple of months, and we think that we could have this

done and ready to go by February.

So, what are the newer things. One is this idea of what can we do to help with the environmental scan. So, as you all probably remember from August, we have asked Alex Kemper and K.K. Lam and their group to do an environment scan about long-term followup. And, so the basic idea of this would be documenting current activities and identifying key gaps for newborn screening conditions -- the idea being providing information for stakeholders.

One of the things we noticed as we've been doing a lot of this stuff -- for example -- on the Quality Measures report is that there's actually a lot of stuff happening, right? That report is 26 pages because there are many examples of people doing this work. But, they're sort of piecemeal. It happens in some states and not others, some regions and not others, some are about treatment, some are just about following and seeing what happens. So, there are a lot of things happening, but it's not really in one place. And, as we spent some time yesterday, we realized that there is value in an iterative process between our workgroup and what Alex and K.K. are doing that we can sort of inform each other and go back and forth. Their report is supposed to be done by July of 2018, so we think that over the next 6 months or 8 months really working with them would be an important way to make sure that what their report comes up with really does meet the needs of our

Committee. And, we think also it will probably tell us a lot about where the key gaps are that we can move forward on. So, I think that's one thing we would really like to work on for the next 6 to 8 months.

Just to remind everyone that for a long time, the Secretary's Advisor has had in some sense what our vision is for long-term followup. And, here is the Hinton, et al paper from 2016. I've shown this to you several times before. If you look on the far left where the outcomes are -- I mean -- here are the things that we want. We want improved survival and well-being, and we have specific measures. And, it goes through how we would get to that and even some of the specific concepts that we would measure.

And, in our Quality Measures report, we looked at what are the specific measures we want to use.

So, what keeps bubbling up though at pretty much every meeting for the last year, it seems, is almost no matter what topic we touch on, people start saying, well we really -- we don't have the whole thing together. There's this happening there, and that happening there, and there's a sense of frustration that we really don't have a handle on it.

So, we can thank Joe Schneider for saying this out loud, but he had this idea of well, it's not anytime soon that we're going to have a single organization that takes responsibility from beginning to end. But, we could imagine

sort of a federated system where maybe the State Newborn Screening Programs have some responsibility, and NewSTEPs has this responsibility, and Patient Registries fit in here, and you could imagine sort of putting together a quilt-like pattern that created a more or less system.

So, our idea for this workgroup -- for now, we'll just call it a road map -- and the idea would be trying to get to someplace where we could say here is what we think are the roles of all the different pieces in the federated system looking at long-term longitudinal lifespan followup -- however you want to think about it. And, again, the gap is that there are lots of things happening. We also know there are a lot of gaps, and there's no real system. There's -- for example -- not a clear way that each of the different parts of the system communicates with each other.

So, what we imagine doing over -- and I put December 2018 as a timeline because we think this will work in some ways in conjunction with the environmental scan -- is can we continue to work with stakeholders, many of whom are represented in our workgroup, and start laying out what this road map might look like and say, we know we want this kind of federated system. Here might be the next step for Newborn Screening Programs, here might be the next step for NewSTEPs. Here might be the next step for different pieces of the system.

And, I also don't want to lose track of -- as we

have this grand vision for where we want to go -- that there might be some interim steps. And, one that came up a few times is, is there a way to explore how to support parent/family/patient registries as a way of more quickly -- as least for some conditions -- getting to where we want to go.

So, I think that's basically what I wanted to say. So, it's open to questions or comments.

DR. JOSEPH BOCCHINI: Thank you, Jeff. This is open for questions and comments. Cindy.

DR. CYNTHIA POWELL: Cynthia Powell. I think this work is so incredibly important, and you've already done a great deal of work -- you know -- on this. But -- you know -- when you look at states that are doing long-term followup and those that aren't, it all comes down to the money. And -- you know -- there's a lack of people to enter data in states that aren't doing it, and the states that are -- you know -- they may charge extra for their newborn screening fee in order to pay for this. And, so I think -- you know -- while I agree with all the different aspects that you've outlined, to really focus on the need to do this. And, I think if -- you know -- State Newborn Screening Programs and State Public Health Directors -- you know -- can hear this from this committee that -- you know -- there needs to be funding to do the long-term followup, and then to make sure that there is an appropriate system to -- you know -- share this information.

DR. JEFFREY BROSCO: So, as you might imagine, this came up yesterday, and pretty much comes up each time in that one of the gaps we have identified across whether it's -- you know -- developing new Quality Measures. Whether it's entering data, whether it's connecting datasets. The resources do matter. And, whether it's -- you know -- funding particular personnel. So, we have identified this many times. And, the question is how best to get to that next step.

We have been discouraged from the idea of just saying, hey, you -- and pointing our finger at someone -- you should put more money into this. That doesn't seem to be within the purview of what we would want the Advisory Committee to say. So, we have been thinking about ways around that. And, so -- for example -- in the Quality Measures report that we're finalizing, we will talk about gaps in funding, and we will talk about how the efforts that have been successful have been properly funded and how they have. And, we will look at what specific next steps -- a couple of concrete things we might be able to do. And, I do think this fits into this idea of the road map. If we can say, all right, Newborn Screening Programs, we think this is where you fit in. You know -- NewSTEPs, this is where you fit in. Then, we might have a clearer idea of what the specific ask is. Because it may also be that we say to AHRQ, look, you guys really need to develop some specific Quality Measure for particular conditions, and we

need to do that too. So, that's -- I hope that we can get there a little bit, but I don't think it's a thing we can go straight at as much as many of us would like to.

DR. JOSEPH BOCCHINI: Okay. Sue Berry?

DR. SUSAN BERRY: This is Sue Berry. Thank you, because I think that's an echo for all of those of us who care for children and who really see this as a burning need. The resources simply aren't there to accomplish the goals. I don't know how we make that a higher priority, but I think that's our -- that's our dirty little secret. It's our shameful gap. I mean -- we keep adding things, we keep doing new stuff -- but, we're not actually fulfilling the responsibility we had initially to a whole group of people that we've identified with these disorders in terms of saying we did newborn screening and it helped them.

So, I'm going to editorialize that way and say that we have to find a way to make this a higher priority.

DR. JEFFREY BROSCO: I'm sure that if Carol were able, she would point out that it's also about treatment, right? And, then when we talk about long-term followup, we mean treatment swell, and that needs to be part of our discussion, especially when it comes to funding. And, I got your name right.

DR. JOSEPH BOCCHINI: So, Carol, Jeff made your comment for you?

DR. JEFFREY BROSCO: Sorry about that.

DR. JOSEPH BOCCHINI: All right. Okay. All right. Then, we have Scott G and Beth.

DR. SCOTT GROSSE: Thank you. Scott Grosse. As an economist, I'd like to point out that there's unlimited wants or needs, and scarce resources, and it's all about tradeoffs, and how do you persuade people that something is worth doing? You should show value. We need to document how long-term followup has improved outcomes or shown value in states that have done it and also show how much resources were used in those states to present that information to other states who might consider it.

DR. BETH TARINI: This is Beth Tarini. I think on both of those comments, I might push the Committee to come up with a statement of Newborn Screening Program priorities because I think there are too many balls in the air. You cannot do all things extremely well. You must decide -- and decisions are difficult -- resources are finite -- opportunities are endless. You must decide what you want to do and how well you want to do it. So, if timeliness -- not to have a spoiler -- is -- if timeliness is our priority, timeliness goes to the top -- to the list of top things. It doesn't have to be one thing, but the list can't be 20. There must be a small and non-exhaustive list of what we believe are the most important and critical challenges facing newborn

screening systems today, and those are the ones that we -- you know -- like no child left behind -- it will not be left behind. And, that is what I think the Committee needs to -- I think would be helpful to have the Committee weigh in on to say these are our urgent mission items. And, these others are ones that are important, but they are not where we are right now. These are the more urgent items.

It will do two things. It will stop the constant moving of, no, it's about timeliness -- no, it's about long-term followup. It will make us focus, and then it will put a time limit upon us to track our progress.

So, I advocate for this to come up if not this coming meeting, in the next meeting or two.

MS. JOAN SCOTT: I think one of the ideas behind doing this road map was to identify all the other stakeholders who have a stake in this issue because it is so critically important, and we have been talking about it with the Committee for a long time. And, if it can't be done all within the Newborn Screening Program, who are all the other players in here that we could start to tap in to potentially link together to try and get the answers? And, so is there another way of getting to it?

DR. BETH TARINI: This is Beth Tarini. I agree, but I would push back that I don't think this is critically important. And, the reason I don't think this is critically

important is because we do not have a letter to the Secretary like we do for timeliness. Am I correct? So, I would argue critically -- with all due respect -- is too strong for long-term followup, given our actions on this Committee. I would say this is an important issue that keeps coming up that we wish we could do more on, but we have not acted as we have with other things like mandated disorders and timeliness. The reasons why -- we could discuss that in a separate discussion -- but, I would argue it's not critically important. I would argue it's important and we're exploring it. But, this is the difference that I'm talking about. This doesn't rise -- this has not seemed by interpretation of our actions to rise to critical like others have. I'm not saying it shouldn't -- I'm saying we need to decide if it should, and then apply the appropriate resources and efforts to achieve a specific goal.

DR. JEFFREY BROSCO: So, just to be clear -- when we talk about long-term -- this is not just about data and how things are going. This is about families not being able to get medical foods for treatment of PKU.

DR. BETH TARINI: I agree.

DR. JEFFREY BROSCO: And, well, no -- it sounded like you didn't. I think almost everyone here would say the fact that we have conditions on the RUSP and people who may or may not be getting appropriate treatment as part of their long-term followup is essential to what we do.

DR. BETH TARINI: I think it's essential. I don't think -- this is Beth Tarini -- I don't think we as the Committee -- there's a different between what is ethical and what is essential. And, what we as the Committee have chosen to devote our focused resources to doing with all of our might, if you will. The State of Iowa's Formula Program -- eliminated. Eliminated. Am I correct when I say eliminated -- like gone -- zero? Those children -- that milk program does not exist. We are not discussing it. We are not discussing whether or not -- we have tried, and we have discussed it, and we have done our best. But, my point is -- these are all important, but I think the Committee needs to put its flags in the sand on what are going to be its top priorities and -- and what are it's goal achievements, and they must be specific, and they must be achievable, and we must put a force behind it.

I'm fine if it's long-term followup. I'm fine if it's medical foods. I just want something, and I want it specific.

DR. JOSEPH BOCCHINI: Carol?

DR. CAROL GREENE: At the risk of repeating, we do -- and Jeff said it very well -- sometimes we say long-term followup, and all of a sudden many people in the room are talking about data collection. And, long-term followup has been defined by this Committee.

And, I -- I think I agree with what I'm hearing

about the importance of the Committee deciding where there is work that the Committee can do that will make a difference. The reason this road map idea keeps coming up is because there's always something pulling to this task and this task that somebody's asking for, and this idea keeps coming back because this is what we don't have for the Committee to then say, what are all the pieces, what are all the goals -- that if we take a little bit of time and write down who are all the stakeholders, what resources are brought to it -- let' -- we've honed in on the outcomes data, we've honed in on the labs, we've honed in on the diseases. But, let's look at the whole picture and say, what does the system look like, what are the parts of it, who are the stakeholders in it, and then we can identify where the Committee wants to work next. Because we've just been sort of taking that -- that next piece, and some of us do keep coming back to treatment. And, we know that we can't say who should pay or should be responsible, but at least if we look at that -- that's why the road map idea keeps coming up. It's let's look at the big picture so that then we can have the Committee make a weighed, informed decision about what needs to be looked at.

So, I hear the plea to work on what's important, and I think we've done a lot of infrastructure, and I think this is needed so that people can decide what's important without just taking the low-hanging fruit.

DR. JOSEPH BOCCHINI: Sue?

DR. SUSAN BERRY: Sue Berry. I hear exactly what you're saying, Beth, which is that many of the actions -- I mean -- speaking as a new member -- my observation has been that we've reacted to things that were pushed upon us like timeliness. We were mandated by legislation essentially to tackle timeliness, so that was a task that was of necessity required of the Committee -- a hundred percent -- we had to do it, right? We are mandated to look at adding new disorders, and we cheerfully do that on a regular basis -- you know -- like clockwork. And, we don't spend very much time about saying whether we should keep doing that, but we keep doing it.

We have other knowledge of the system that we know are parts of what should be accomplished, but nobody's ever said, this is your task. You must do it. I would say the one element we've worked hardest on -- because -- I mean -- it comes down to my personal knowledge of it -- is medical foods, and the Committee has acted on a number of occasions on at least that element of treatment.

But, as a general rule, we haven't -- a hundred percent I agree with you -- we talk about it, but we've never actually done anything to say this is so important in the system that we have to fix it. And, part of it is that there's no easy locus for long-term followup. So, it's hard to assign that responsibility. We know that's the State Newborn

Screening Program's job to implement screening. We know that it's the Committee's job to brief and think about new disorders. When we get handed a task like timeliness, timeliness becomes the task.

But, there's no -- no one who is singly responsible for long-term followup and treatment. It's the clinicians, ultimately, who are, and we're just all going "Aaah, aaah!" okay?

So, how do we find that locus of responsibility, and then -- so maybe the road map is a way to do that -- and, then how do we -- you can't do it all at once. How do we parse it out?

DR. BETH TARINI: Exactly. Because we -- what I predict could happen is that a lawsuit occurs from a long-term followup -- as we do much in health care -- in the health care system -- and a crisis creates our action. And, so I'm not saying that -- and, that's how we'll find our locus -- and, I'm not saying that this is coming up during the long-term followup discussion -- I'm not saying that the road map is not a good place to start. I'm saying we tend to wallow in exploration, and, then perseverate and paralyze when it comes to a decision on where to identify the locus of action. That's where I think we as a Committee need to do a little more work. You disagree.

DR. JEFFREY BROSCO: I don't really understand because it sounds like on one hand you're saying we have these

very precise things we do and we haven't taken action here, so we said, well, we want to see the whole system, figure out where to really focus our energy, and now you call that perseverating. So, I don't know which --

DR. BETH TARINI: Okay. I'll try to clarify. That's helpful. So, what I'm saying is perhaps a synergy of what Sue has said as well. We tend to be reactive. We tend to make great strides when we're reactive for the following reasons, possibly. We are forced by mandate, by scrutiny from external entities -- including the media -- and mandate from our legislation to do specific actions. We therefore martial much resources and money from our Federal partners to address these issues, and we make great progress, as we saw yesterday with Josh's presentation.

Those tend to be reactive. They are not preventative medicine or preventative public health.

In other areas, we tend to wallow for years about issues -- I think your road map actually sort of puts us in a place where we can now -- and, again, this is why I'm trying to separate it from the road map -- that we get to a position where we've had these discussion for upwards of a decade, and we have not made progress because we can't get to the point of preventative identification of the locus that this needs to be done and the priorities, and then martial our resources according to them.

Now, that comes at the largest point of long-term followup, and then the precision point of where in long-term followup. I think the road map is an excellent point of getting to the inner locus. What I'm saying is, we can't do everything, so we must have at least focused -- we must have focused discussions on what is going to be our lever. I'm happy to discuss after if it's not clear.

DR. JOSEPH BOCCHINI: So, before we take that question, let me just clarify the record for timeliness. The issue of timeliness came to our attention by a parent who on -- during public comments indicated that there was an issue in the state related to her child receiving a diagnosis before symptoms developed. And, this Committee chose to look into that. Subsequently, Congress put that on our re-authorization as part of our responsibility. So, sometimes things come to us because of issues that are identified by the public or by others that we then take on and actually we already had timeliness requirements for the Newborn Screening Program, which we then found out were not being met by all states, and that led to a revision and reworking with them.

And, I think other things are going to come to us based on the system perhaps having gaps or barriers or things, and so we do need to be reactive in that sense to address those issues when they come up.

But, I understand the importance of us being

proactive as well and attempting to identify issues that we view as important for the program or coming up because of changing technologies and other things as well. So, I think looking to try and strengthen the activities of the Committee by using the expertise around the table is really important, and we need to do that.

DR. BETH TARINI: This is Beth Tarini. Just to clarify. I didn't mean to say we were without action, but our action became much -- I remember that parent very well with the postal service story. She came, I believe, three meetings in a row. Our attention became much more vigorous after the Milwaukee Sentinel article, and so that's the type of shifting in enthusiasm/energy that I'm thinking about.

But, I do -- I do agree -- to correct myself -- we were actually discussing timeliness at that point when it was brought up in the public forum.

DR. JOSEPH BOCCHINI: So, let's see. I have Dieter and then Cindy.

DR. DIETRICH MATERN: Yeah, Dieter Matern. Thanks, Joe, for clarifying how we got to timeliness.

The product of that was eventually a recommendation to the Secretary of what should happen. And, I think as we have these workgroups -- and I think the workgroup apparently though that this was a worthwhile project -- and, I think there's no one in the room who wouldn't agree with it, I would

suggest go ahead, do this work, and then in the first meeting in 2019 the latest, there should be a vote as to whether the recommendation should be made to the Secretary as to what long-term followup entails. And, then have the Secretary figure out how this can be -- how the states can be incentivized to actually follow through with that.

I don't know what other projects you want to have prioritized. I don't know if we have a list of all the projects that we actually can see what is currently ongoing and what might be in the parking lot or wherever.

DR. JOSEPH BOCCHINI: Okay. Cindy?

DR. CYNTHIA POWELL: Cynthia Powell. My concern is that -- you know -- we don't even have good consensus on standard of care for many of the conditions that we've been -- you know -- screening for many, many years, let alone this new territory that we're getting into with conditions that have recently been approved where 80% may have -- you know -- adult onset. And -- you know -- the Committee is asked to make a decision, and -- you know -- with very little time, with very little evidence, regardless of the excellent job that Alex and K.K. do in gathering all that evidence. But -- you know -- we make a recommendation, and then we have no idea really what -- you know -- the outcomes are. And, as a clinician, I really fear that we could be doing much more harm than good, but I don't know, and I don't know how we're ever going to get that

information unless we do in some way prioritize the need for long-term followup.

DR. DIETRICH MATERN: Dieter Matern again. So, I agree with that, but I think the work here must be more general as to what is long-term followup. I don't think it can -- within scope -- you can't put the exact treatment of any -- every condition we have and every variant thereof. I mean -- I think there are other opportunities, other organizations, who should be working on this. We see guidelines coming out for various conditions that are included in Newborn Screening Programs as to how they should be treated and followed up, and I think we should encourage those entities to continue providing those.

DR. JOSEPH BOCCHINI: Okay. Are there additional questions or comments? Yes, Sue?

DR. SUSAN BERRY: Just a final word. Sue Berry here. Cindy, I think that's the key to it, which is that unless we have systematic plans for long-term followup, we won't be able to answer the question that you raised. I think Dieter's suggestion about making that a higher priority and planning the road map for how that can be accomplished is the strategy that can be followed. And, I think that is a task in my view that the Committee can -- we can have a document that says, here's what's long-term followup, here's what our responsibilities are, here's some strategies for

accomplishment. And, I think that's a quite laudable goal that the Committee could endorse. And, it could take the form of a letter because that's our means of communicating.

DR. JOSEPH BOCCHINI: So, Carol?

DR. CAROL GREENE: Just appreciating and anticipating what the charge might be. If you could go back a couple slides. I think forward one. The table from the paper. Okay.

In the idea of a road map, the road map would not be about -- or at least as I understand the concept -- it would not be about defining what is long-term followup. This Committee has defined it. This would be a road map of what's going on around that definition. This Committee has gone on record -- long-term followup is defined and it's right up there.

DR. JEFFREY BROSCO: So, to sort of conclude in followup on that, I think it's worth pointing out sort of our process, which has been that at our last few meetings -- but particularly on our phone calls and this meeting -- we've asked our workgroup, what are the big issues out there? What are the things we really need to tackle? What are the most important things? What do you see in your practice? What do you see as a parent? And, the list is about 13 or 14 things long. But, we also realized that as we start looking at any one of those, there's a lot more happening than we think. And, this fits in

very well with the environmental scan that we asked Alex and K.K. to do, which is -- there are lots of pieces of this already happening, and it really came together saying, we need to step back, make sure we have all these pieces together, know where the true gaps are. And, the idea of a road map is, what specific things can we do to get to this.

So, I think that, Beth, we're trying in some sense. You're right. There's a political process where you react to some things because things happen, and there are the legal issues we have to follow. And, this is some sense an attempt, I think, to do what you suggested, which is take a step back, find out really what is happening and what the true gaps are, and the next steps for that. So, I hope that we're able to accomplish that, and you'll be happy with us.

DR. JOSEPH BOCCHINI: So, thank you, Jeff. My feeling is the consensus from the Committee is that this should go ahead, and that the workgroup should proceed with this road map development. I'm not sure, Dieter, that they could provide a final product that would be voted upon in February, but -- 2019. That would make better sense, thank you. Okay. All right. So, is that the general consensus to go forward? Nodding yes. Okay, thank you. All right. Thank you, Jeff, and thank you for the workgroup members as well.

So, next we have the presentation from Laboratory Standards and Procedures Workgroup, and Kellie Kelm, the Chair

will present this. Thank you.

DR. KELLIE KELM: Good morning. We had a really interesting meeting. We had a little hard time. We were really continuing a lot of the discussion during the Committee, and so it was a quite interesting discussion that we had.

So, this is just our agenda, briefly. And, we did really spend a lot of time talking about document on cutoffs as well as timeliness, and so unfortunately our discussion on priorities was short. But, I think that that was still time well spent. How can I move forward?

So, this is our workgroup roster, currently. And, you can see the Committee members that are in bold. We welcomed Scott Shone to the workgroup, and we do have three members rolling off. They couldn't join us yesterday. They was Harry Hannon, Joann Bodurtha, and Koon Lai, and we are looking forward to having some new members join us in February.

This isn't going forward. It's not moving. Here we go, okay. So, first we had an update from Joe Orsini on the work that his sub-committee is doing on the guidelines for determining cutoffs, which has been continuing from some of the information that concerns some of the articles and obviously in parents and moving forward into a guideline that APHL is taking on.

So, we had an update on the outline of the document. This just doesn't like me today. All right. Next slide.

So, as I said, following discussions on cutoffs at the national level, the sub-committee has been tasked with developing this guidance on how to determine cutoffs using newborn screening. And, so Joe gave us an update on where it was, so the draft has already been reviewed by the APHL Newborn Screening and Genetics in Public Health Committee, and they had a lot of feedback from that group. And, he presented some of that feedback that they had received, and I'm not going to go over that here, because I think what I'm going to do is provide their overview -- sort of their outline, and then some of the feedback that our workgroup gave to them during our discussion yesterday.

So, next slide. So, I have two slides with the current outline of the document, so I just wanted to state again here for you what the purpose of it was. So, there is a lot of information on historically how labs have been determining cutoffs. And, so that is described here as the purpose.

Next slide. And, then there were these additional sections. So, our overview of cutoff determination -- that's going to be the sort of description of the general process, historically has been used. Third section is cutoff considerations for specific newborn screening disorders. And, number four is monitoring and evaluating the cutoff. And, then last is going to be the list of references.

Next slide. So, some of the feedback that our workgroup was giving them based on the presentation was there was some concern that the document was a little bit too heavy on history and what's been done before. So, are we going to need more -- another document that's a guideline, because we felt that was missing. But, I think the suggestion was that we felt there needed to be more information included in the document about other methods that could be used to calculate cutoffs, and that includes multiples of the medians and the clear tool, pros and cons of historical as well as some of the newer methods. So, I think the workgroup felt that if there was a lot more information added to the guideline, that it would be a guideline. Otherwise, it would be a little bit too much of just a historical document.

The other ideas included incorporation more information from the CAP checklist on cutoff determination in this document.

Next slide. The other thing that was mentioned was more of a discussion of using goals for sensitivity and specificity when choosing cutoffs, and -- you know -- assessing the impact of false positives and false negatives as you consider your cutoff. And, that was something that we thought could be folded into the document more. And, then factors that impact cutoff determination. So, we know that states may choose how well -- you know -- where there cutoff and what the

goals of the cutoffs are depending on -- for example -- if they have second-tier testing. So, they might shift it to actually have more false positives because they're going to use second-tier testing. What conditions you're screening for. So, different states have different goals in terms of -- you know -- what their goal is in terms of what they want to capture. And, then, of course, some states one screen versus two-screen states also have different goals for their cutoffs. So, I think that that was our main feedback that we gave Joe and his group.

So, next slide. So, these are the next steps and estimated timelines. The APHL Hemoglobinopathies Workgroup is going to add some work this month, and the goal is to then send out the draft and solicit feedback from the newborn screening community including our workgroup in the next month or so, and then incorporate that feedback from the community into their final draft with the goal of presenting the draft to the Committee in February.

So, it is -- you know -- it's going to be quite tight in terms of getting -- you know -- sending it out and getting workgroup and other group's input in the next month or two.

Next slide. So, we did wind up having after the presentation yesterday on the timeliness data -- so, one of our workgroup projects has been to look at sort of the timeliness

data and assess -- you know -- and assess the data and think of some of the impacts of -- for example -- what were the consequences of improving timeliness, etcetera. And, so some of these things we already sort of talked about yesterday, but, obviously, once again we brought up the switch from 24 hours to 2 days in the NewSTEPs data collection for transport to the lab. And, we had some other really interesting discussions, and some of it we even touched upon earlier today in some of the other workgroup things. So, looking outside Newborn Screening Programs to assess the whole system. So, timeliness, we really focused a lot on what our labs can do, but some of the discussion has been about, well, what about downstream short-term and long-term followup -- you know -- and things like that.

There was also discussion about -- you know -- we've really been focusing on reporting presumptive positive results within 5 or 7 days, but if it's the weekend, and it's really not a time-critical condition, then it might not make sense to -- you know -- put the family in a lot of anxiety, calling them immediately on the weekend, if it's something where -- you know -- we don't need to get them to the ER immediately versus a time-critical condition.

So, standards for other timeliness pieces, and this has come up before. Obviously, we've even talked -- tried to talk to Joint Commission about -- you know -- getting their

impact in some of our timeliness issues that we wanted -- not just this Committee -- but for other groups to help us with, and that's been a struggle, but that's come up again. And, obviously -- you know -- once again, what is this set up for? What is the goal? Are we meeting the goal, and how can we improve?

So, Committee -- one of the thoughts of some of the members was the Committee could consider recommendations for other parts of the system outside of lab. I mean -- I think that discussion we just had -- it played right into that. And, also, can we link -- you know -- these improvements in timeliness in improving outcomes? That's the big picture. Can we do it? But, I think discussing like we just did about long-term followup and measuring those pieces and the struggle to do that -- you know -- sort of -- that would be hard to do.

Next slide. So, when we had unfortunately a very, I think, 10-minute window to think about future projects. And, the next slide, I think we have our -- this was our charge that we've had for the workgroup -- you know. And, so we've looked about lab procedures. We've looked at infrastructure and services.

And, next slide. So, this is our -- you know -- the last project that was assigned to us. So, first of all, exploring the role of NexGen sequencing in newborn screening. And, so we've had -- it's sort of been something we've been

monitoring. We've had presentations. We've had -- you know -- updates from things that are going on in NGS. And, I think that the -- you know -- we still had some other things that were coming up with NGS and even just generally molecular testing in newborn screening that are still coming that we want -- that we felt was still a role for us.

And, so the next slide has sort of updated our proposal for project 1 would just be maybe even changing NGS to molecular tests. And, so still understanding how molecular tests are going to be used. And, we had heard -- not yesterday but previously -- that there was some more discussion about molecular first-line tests, and I've added that to the bottom. Michael Watson has talked about some work that's being done. We know the Insight projects are still ongoing, and it would be great to hear an update. Molecular tests being added for second-tier tests. And, I think -- the other thing we thought of is also falling underneath this as well as we hear more about other types of second-tier tests that are being developed. And, obviously, use of tools and other things as well. So, this was our idea to continue sort of project number 1, expand it a little bit, which I think in general sometimes we do, because we still think that there's a lot of information on molecular tests that's growing that our Lab Workgroup should keep touch on.

Next slide. So, project 2. That was assigned to us

in 2016. It was reviewing the timeliness initiatives and the data that was emerging. Unfortunately, the data really just did emerge, so we have heard some talks from California -- for example. They've published data on the implications of their earlier specimen collection, and I think if there is additional data, we can hear about that as well as considering -- continuing our discussions on timeliness and what states are doing, and what we can do in terms of obviously laboratory and maybe beyond.

So, next slide. So, we really felt that we should continue to monitor timeliness. We did have some other ideas that were brought up. We didn't have a lot of time to flush them out. So, some of the discussion was -- you know -- as states are bringing on the new conditions that are added to the RUSP -- you know -- they are taking -- you know -- they are obviously rolling out slowly in many states. So, some of the discussion is does it make sense for us -- because we don't as a Committee often talk about it -- does it make sense for the Lab Workgroup to talk about barriers, and do we have a role in discussing what is leading to the fact that there is very slow uptake for some of these tests, and that obviously -- you know -- pilots -- which has come up before -- we've had many discussions about it, and obviously -- you know -- we have an organization whose goal is to start doing more pilots. And, we have a new Committee member on a workgroup who's in touch with

that as well. But -- you know -- that's something we could still maybe talk about, but I think we through projects 1 and 2 should continue unless people had thoughts about other things we could do. So, that's it.

DR. JOSEPH BOCCHINI: Thank you, Kellie. This is now open for questions, comments, and discussion. Natasha?

MS. NATASHA BONHOMME: Natasha Bonhomme. I have a question about the presentation that was done around cutoffs. Is that okay? I saw the outline, and I think that was really helpful. In any of that, is there any discussion of how this would be communicated out to the public or just out beyond kind of those who are in the labs doing this work? And, I bring that up because though the discussion of cutoffs has been around for years, it really got taken to another level due to a news article. And, so I'm just thinking in any of that, is there a component of actually communicating it out to probably those who have a lot of questions about what's happening with cutoffs.

DR. KELLIE KELM: I think right now -- I mean -- we didn't. I think mainly our focus was giving feedback to the APHL sub-committee that was working on it. But, obviously, I don't know if APHL or the Committee has thought about something beyond the document right now.

DR. JOSEPH BOCCHINI: Susan.

DR. SUSAN TANKSLEY: Susan Tanksley. So, Natasha,

that's a good point, and I will bring it up to APHL and the sub-committee, and we can talk in the Committee as to how something like that -- how we might be able to accomplish something like that.

DR. JOSEPH BOCCHINI: Dieter?

DR. DIETRICH MATERN: Dieter Matern. I think we gave, however, a suggestion back to Dr. Orsini that the document should include generally understandable language about the terms that are used. And, my assumption would be that the document would be available to the public online. Whether APHL will make any special announcement, press release, whatever when it's out there is a different question.

DR. JOSEPH BOCCHINI: Okay. Other questions or comments? Dieter?

DR. DIETRICH MATERN: Dieter Matern again. You mentioned, I think, the review of the RUSP. One of the things that came to attention again at the recent APHL Newborn Screening Symposium was that we still don't have on the website -- the Committee's website -- an option to reclassify a condition that is on the RUSP to either get it off the RUSP completely to get it downgraded to secondary target, or something upgraded to primary target. But, again, this is, I think, important because at the APHL meeting, there was at least one presentation, I believe, from Michigan about how they get rid of SCAD deficiency and IVDH deficiency. So, I think

that is important, and I would rather have the states that want to remove stuff come back here and basically ask for that in a more official, formal approach so that we can have an evidence review whether that should happen.

DR. JOSEPH BOCCHINI: Yeah, and I think that's a good point. And, I think that probably we need an ADHOC Workgroup of Committee members and others to address that issue. And, I know we've talked about it, but I think you're right. It needs to happen. So, that should be on our going-forward agenda. Scott?

DR. SCOTT SHONE: Scott Shone. I've been toying with whether or not to say this. But, I think Natasha's comment gets at sort of something bigger that just sort of -- now being part of the process here has occurred to me -- is that a lot of these projects are cross cutting. But, because of the way the workgroups are structured, they tend to be a little siloed. And, so timeliness ended up being a laboratory -- Laboratory and Standards Workgroup topic, but there were educational components that then the Laboratorians were tasked with. And, there were followup -- you know followup issues that -- but it still stayed in that workgroup. And, then around cutoffs -- the same idea -- you know. And, I think -- I haven't seen the document yet, so let me be clear. But, I saw the slides that Joe presented yesterday, and it's -- it's largely written by Laboratorians for Laboratorians. So, just

publicizing and communicating the existence of the document doesn't mean that it's going to effectively communicate the message of, this is why the system does what it does and how it's been designed to function in an optimal screening fashion, which is why just the simple historic perspective might not get at the goal, because part of the challenge was -- is the way we've been doing it the right way to continue doing it.

And, so I wonder -- and, this is not just a Lab Workgroup issue -- but, I wonder if the Committee needs to consider how to ensure that these endeavors were undertaken, and Beth's comment about priorities really gets at that. A lot of these things are cross cutting -- you know -- the paradigm is completely changed in this system, right? It's no longer PKU with medical food, which we still haven't gotten done or galactosemia or whatever. It's -- it's much more complex. And, until we start thinking about these as opposed to a lab issue, a followup issue, an education issue, as a system issue -- I'm sorry to sound like a broken record over the last two days -- maybe I'm not going to be invited back in February.

[Laughter.]

But, the fact is, we want -- it sounds like we want to move the ball forward substantially on these issues, not because -- we don't want to, we need to. And, if we just think about it as the Committee -- you know -- NewSTEPs, NewSTEPs 360, APHL, and all the groups were represented at the table --

not just this U-shaped table, but the tables out there -- then, we're not going to have the significant outcomes we need for the system.

And, so my recommendation is part of the process of deciding what the priorities are for the workgroups will be, how do we integrate the workgroups either whether it's at this table, or how do they integrate, so that -- so that we get the biggest bang for the buck. You know -- HRSA and the Regional Collaboratives, now the Regional Genetic Networks -- there was a requirement that there by multidisciplinary projects. You know -- NIMAC did a great job of this over the last couple of years. It was an honor to be part of that in my role in New Jersey working with Michele and these cross-cutting projects that helped -- it wasn't just one issue -- you know. It was an issue that was tackled from many fronts. And, we were able to get more done that way as opposed to we have a document, and we educated some hospitals on how important newborn screening is so that they actually package this right, but actually, oh, by the way, the Secretary of Health -- you know -- thanks to efforts by the Secretary of Health who understands how important this is and established a timeliness Czar. Maybe it's not just for newborn screening but for the entire public health lab so that the benefit is shared while the cost is minimized -- something like that. And, I think that's where we need to go with our thought processes.

DR. JOSEPH BOCCHINI: Thank you. Beth?

DR. BETH TARINI: This is Beth Tarini. So, I think that I agree with you. We are siloed and have work -- I believe -- because we have workgroups that have sort of been created based on topics, not on problems -- largely. We have had these ADHOCS as problems come up. So, I wonder if we need to diminish in some way the roles of these standing workgroups, which are created just based on an organizational cut and aren't based on -- they're not problem focused. If they're problem focused, they're focused on a problem that's been prioritized, and then they are cross cutting because the members involved have specific skills and/or content expertise and/or connections related to that.

So, when you create AHOCS, you then create a prioritized group, and you bring together by nature of the creation a cross-cutting, multidisciplinary team. What I feel like we're trying to do now is find projects and put them in the buckets of the existing workgroups, and that is the system we have designed -- this microsystem -- is potentially working against us being successful. And, exactly as you point out, we are actually not working like a system. We are working as individuals trying to make it happen.

DR. JOSEPH BOCCHINI: Thanks. Mei?

DR. MEI WANG BAKER: Mei Baker. I just want to go back to this document for the cutoff evaluation. I think the

intention is to provide a deadline because historically we do. But, now how we systematically end up with some guidance and some standardization -- that's the purpose. Also, I just -- I really -- I'm glad actually that Scott mentioned that because that is intention for the laboratory practice. I'm not so sure how beneficial is it to the public, but I think public needs to know the measurement it has been taking. I think that's important.

The one thing -- I want to add on one thing is at our meeting, we talked about looking at all the different practices, and also we want to cross check with a certain like a CRS document, and also even clear [inaudible] requirement. So, this way we are really in the position because obviously this discussion is the patient's safety, right? So, I think we need some -- you know -- to follow certain procedures. We talked about how you set a cutoff and what kind of tool you use. You need to state in your [inaudible] require you to do periodic assessment and monitor when you do that. I just wanted to add this piece.

DR. JOSEPH BOCCHINI: Susan?

DR. SUSAN TANKSLEY: Susan Tanksley, APHL. So, Jelili made me aware that there has been a 1-pager on the APHL website regarding cutoffs since the issue came out many, many months ago at this point. But, that is a document. So, it's publicly available now, but it's something that we could use.

Mei is correct when she says that this is a technically written document, and its intent and purpose was for the laboratories and helping them to figure out what are the best ways to establish cutoffs or reference ranges or whatever we're going to call them. But, we can build off of what's existing now as far as what's publicly available, and we can also work with Genetic Alliance in some kind of document that we could share so that it's available in multiple areas.

DR. DIETRICH MATERN: Dieter Matern. So, the document that has been drafted or is almost ready and that we discussed yesterday is really an overview of what -- how things have been done, and it is pointing out to whoever wants to read it what the options are to determine cutoffs and reference ranges, and so on. I don't believe it is really -- it clearly is not -- and, Joe said -- it's not an SOP as to how to establish cutoffs and reference ranges, which -- I think -- is really what laboratories need versus what it is. But, I think that the idea was that that would be a subsequent document. But, maybe that is something that our Committee should actually take the lead on and try to put together.

DR. JOSEPH BOCCHINI: All right. Any additional questions or comments? All right. So, the consensus again would be to continue the work that you're doing, and other comments? Okay. Thank you, Susan, and the rest of your workgroup. Thank you.

So, we are actually 7 minutes ahead of time. All right. So, we have an hour for lunch with a little extra 7 minutes, and we are going to promptly restart at 12:45. And, since we've completed the discussions about each of the individual workgroups and direction that they're going in, we're going to start at 12:45 with the discussions panel on SCID. Thank you.

[Lunch break]

DR. JOSEPH BOCCHINI: All right. Let's go ahead and call the meeting to order. First item is roll call. So, Kamila is not here. Mei Baker?

DR. MEI WANG BAKER: Here.

DR. JOSEPH BOCCHINI: Susan had to leave us early. I'm here. Jeff had to leave early. And, Scott Grosse?

MR. SCOTT GROSSE: Here.

DR. JOSEPH BOCCHINI: Kellie Kelm?

DR. KELLIE KELM: Here.

DR. JOSEPH BOCCHINI: And, then Debi Sarkar for HRSA?

MS. DEBI SARKAR: Here

DR. JOSEPH BOCCHINI: Dieter Matern?

DR. DIETRICH MATERN: Here, and thanks for the chocolate. Thanks, Annamarie.

[Laughter.]

DR. JOSEPH BOCCHINI: Cindy Powell?

DR. CYNTHIA POWELL: Here.

DR. JOSEPH BOCCHINI: Melissa Parisi?

DR. MELISSA PARISI: Here.

DR. JOSEPH BOCCHINI: Annamarie Saarinen?

MS. ANNAMARIE SAARINEN: Here.

DR. JOSEPH BOCCHINI: Scott Shone?

DR. SCOTT SHONE: Present.

DR. JOSEPH BOCCHINI: Beth Tarini?

DR. BETH TARINI: Here.

DR. JOSEPH BOCCHINI: And, Catharine Riley?

DR. CATHARINE RILEY: Here.

DR. JOSEPH BOCCHINI: For Organizational Representatives. Bob Ostrander?

FEMALE SPEAKER: His jacket is here, so I think he'll be right back.

DR. JOSEPH BOCCHINI: Okay. All right. We won't give him credit. Okay.

DR. JOSEPH BOCCHINI: Michael Watson?

DR. MICHAEL WATSON: Here.

DR. JOSEPH BOCCHINI: Britton Rink will not be available this afternoon.

DR. BRITTON RINK: I'm here.

DR. JOSEPH BOCCHINI: Oh, you're there. Okay, great. Thank you.

DR. JOSEPH BOCCHINI: Kate Tullis by webcast?

DR. KATE TULLIS: Here.

DR. JOSEPH BOCCHINI: Susan Tanksley?

DR. SUSAN TANKSLEY: Here.

DR. JOSEPH BOCCHINI: Chris Kus by webcast?

DR. CHRISTOPHER KUS: Here.

DR. JOSEPH BOCCHINI: Adam Kanis?

DR. ADAM KANIS: Here.

DR. JOSEPH BOCCHINI: Natasha Bonhomme?

MS. NATASHA BONHOMME: Here.

DR. JOSEPH BOCCHINI: Siobhan Dolan?

DR. SIOBHAN DOLAN: Here.

DR. JOSEPH BOCCHINI: And, then Cate Walsh Vockley?

DR. CATE WALSH VOCKLEY: Here.

DR. JOSEPH BOCCHINI: And, Carol Greene?

DR. CAROL GREENE: Here.

DR. JOSEPH BOCCHINI: Great. Thank you.

So, now we're going to begin a panel discussion on the Clinical and Public Health Impact of Screening for SCID. As you know, the Secretary approved the Advisory Committee recommendation to add screening for SCID to the RUSP in 2010. And, as of this past August, 47 Newborn Screening Programs offer universal newborn screening for SCID, and the remaining programs continue to work toward full implementation.

The Association of Public Health Laboratories recently hosted a national SCID meeting for SCID newborn

screening stakeholders, in part to facilitate the strengthening of relationships between the SCID clinical network and a newborn screening community within each state.

So, we've invited three speakers to join us today to provide information on the Public Health and Clinical Impact of SCID Screening. And, as we did yesterday, we'll have the three presentations, then open the floor for questions, comments, and discussion.

Our first presenter will be Sikha Singh. She will be offering an overview of the Public Health Impact of SCID Screening and an update of where the states are with SCID screening, summarizing APHL SCID Screening meeting. Ms. Singh is the Manager of Newborn Screening and Genetics Operations for the Association of Public Health Laboratories, and this has a focus on Newborn Screening Technical Assistance and evaluation, the NewSTEPs program. She joined APHL in 2009 from the Johns Hopkins University, where she gained experience in high throughput genomic sequencing and is a Certified Project Management Professional.

I'm going to also introduce the next speaker so that we can move right along and then let her get started. The second presenter will be Adrienne Manning. She will be sharing with us Connecticut's experience with bringing SCID on to the panel. Ms. Manning is the Division Director of the Newborn Screening Program at the Connecticut Department of Public

Health. She joined the Connecticut Department of Public Health Laboratory in 2004 during the implementation of the Expanded Newborn Screening MS/MS validation process. Ms. Manning was responsible for evaluating, validating, troubleshooting a variety of analytical assays and instrumentation for inclusion and use in the Connecticut Newborn Screening Program, including a screening method for SCID and X-ADL. She is also a member of APHL's Newborn Screening Quality Assurance/Quality Control sub-committee.

And, the third presenter in the panel will be Dr. Lisa Kobrynski. Dr. Kobrynski will be covering the Clinical Impact of SCID Screening. She is a Clinical Immunologist, Director of the Jeffrey Modell Center for Primary Immune Deficiencies. She has over 20 years of experience in the diagnosis and treatment of infants with SCID and other primary immune deficiencies. She is part of a team of investigators at Children's Health Care of Atlanta, who participate in the Primary Immune Deficiency Consortia.

So, I'm going to turn this over to Ms. Singh. Thank you.

MS. SIKHA SINGH: Good afternoon, everyone. Thank you for that introduction. Can everyone in the back hear me? Yeah. Awesome.

So, I want to thank the Committee for the opportunity to share some of the Public Health Impact of Severe

Combined Immunodeficiency in Newborn Screening. I'll be talking about some of the NewSTEPs data demonstrating this to get SCID screening across the country as well as summarizing some of the lessons learned from the recently held SCID National meeting.

Joshua Miller gave a nice overview yesterday of NewSTEPs describing it as the Newborn Screening Technical Assistance and Evaluation Program. It's a HRSA-funded program to APHL -- the Association of Public Health Laboratories -- in collaboration with the Colorado School of Public Health. We function with three main goals, the first being facilitating communication and collaboration within the newborn screening community. The second being operating a data repository to facilitate continuous quality improvement as well as data-drive outcome assessments. And, the third being to serve as a technical assistance resource center.

In addition to the activities of NewSTEPs, APHL was also funded by HRSA in 2014 to offer technical and financial assistance to help expand the capacity of state Newborn Screening Programs to implement SCID.

I would like to mention that this was not an isolated funding opportunity. In fact, prior to as well as following the addition of SCID to the RUSP, there have been a number of national and multiagency initiatives around SCID newborn screening, including through the NIH, the CDC, as well

as other HRSA-funded activities.

However, while the implementation of SCID newborn screening at the state level has been steady, at the time of funding announcement, you'll see the date on the press release of September 2014. Less than half of states were screening for SCID.

The key component of this particular funding opportunity was that APHL issued a competitive RFP and eventually funded 11 states and 1 organization, the Immune Deficiency Foundation, to receive financial support for SCID implementation, education, and network-building activities. These programs were Alabama, Arizona, Hawaii, Kansas, Kentucky, Maryland, North Carolina, North Dakota, Puerto Rico, Tennessee, and Utah.

So, where have we been, and where are we with regard to universal screening for SCID. Prior to the inclusion of SCID on the Recommended Uniform Screening Panel, Wisconsin and Massachusetts were the early adopters of SCID newborn screening in 2008 and 2009, respectively.

In 2010, when the disorder was added to the RUSP, California and New York implemented SCID newborn screening, as well as the Navajo Nation and Arizona.

As time progressed, additional states began to onboard SCID newborn screening. I want to call to your attention that on these maps, there are some nuances that are

not captured. Some states who are not screening are still pursuing authorization or funding or performing validation and pilot studies to get closer to screening for SCID. These nuances -- while not well depicted on this map -- are available in the NewSTEPs data repository and have been carefully brought out and vetted by the NewSTEPs Committee to ensure that the picture we provide to the data is more than just binary and accounts for various stages that fall within the spectrum of not screening to screening.

By 2014, just about half of the states were offering universal screening for SCID. As noted, it was at this time that APHL awarded financial support to 11 states. Those are denoted by a gold star on this map.

In 2015, more than half of states were offering universal screening for SCID.

By 2016, more than 75% of newborns were screened for SCID.

As of current, 94% of newborns are screened for SCID in this country. In the time that has elapsed since 2014, 23 additional states have begun universal screening, and in the time that’s elapsed since 2010, 48 SCIDS -- 48 states, rather are now offering universal screening for SCID.

I want to mention that in the end, the denominator here is 53. We’re including all 50 states, Puerto Rico, the District of Columbia, and Guam.

So, in July 2015, APHL held -- or NewSTEPs rather -- our first SCIT National meeting, which addressed current challenges faced by State Newborn Screening Programs in implementing SCID including the intervention of new technology, laboratory staffing to conduct screens, clinical followup capacity, funding for personnel, equipment, and education, as well as legislative and statutory mandates.

The audience during this National meeting was laboratory and followup staff from Newborn Screening Programs, and at the time of this meeting, 35 states were offering universal screening for SCID.

Two years later, we've come pretty far with 48 states now offering universal screening for SCID.

In August 2017, it was an opportune time to hold another meeting. This time, we engaged both the newborn screening community as well as clinical stakeholders to strengthen the Clinical Referral Networks within Newborn Screening Programs and each state and region.

I'll take the next few minutes to talk a little bit about what we learned from this meeting.

So, as we know, SCID is unique from the previous disorders that have been added to the RUSP in that it requires molecular methodologies to conduct the test -- the screen. I have mixed feelings about this slide. It simultaneously makes me chuckle and also gives me stress-related flashbacks. Prior

to joining APHL, as Dr. Bocchini said, I worked in a high throughput sequencing facility, and every day, we ran PCR reactions, and while we definitely trust the science, we also prayed to the PCR Gods every day.

[Laughter.]

The introduction of PCR into a newborn screening laboratory was certainly not a trivial addition.

During the meeting in August, we focused on the unique challenges associated with this testing, as well as followup policy and education, their challenges, barriers, and opportunities. Barriers for newborn screening SCID policy are not unlike the challenges faced when adding other disorders to the RUSP. This includes obtaining state legislative mandates when needed and also acquiring fee increases.

Of the 11 APHL-funded SCID awardees, 9 required a fee increase in order to support SCID implementation, while 1 of those 11 states has no newborn screening.

During the meeting, states also discussed the challenges associated with insurance coverage for confirmatory DNA analysis as well as for coverage after diagnosis.

Regarding testing, we know that among the primary various implementations of newborn screening for SCID, is a lack of funding to support laboratory requirements to bring on the necessary molecular tests. Many states face barriers to implementation of this methodology due to the lack of trained

staff and inadequate space to incorporate a molecular workflow.

Of the 11 funded APHL SCID awardees, 8 required modifications to their laboratories; 2 of the 11 states don't perform their own testing in house, and, one of the laboratories has recently moved to a new location and therefore are not requiring immediate modifications.

There is also variability in the algorithms used across states. About 30% of programs currently use the FDA-approved kit, and about 70% of programs utilize a laboratory-developed test, an LDT. Of the 11 SCID -- APHL-funded SCID awardees, 3 awardees utilize the FDA-approved kit, 7 used an LDT, 1 program used both. They initially began screening with an FDA-approved assay, and the plan to move to an LDT later on -- early next year, rather -- in order to support multiplexing for potentially SMA.

Molecular testing has also posed a unique challenge regarding the interpretation of these results for followup programs. Additionally, due to the lower frequency of SCID compared to other disorders seen by other groups of specialists, there is a paucity of pediatric immunologists across the nation. Establishing Clinical Referral Networks and facilitating relationships between program staff and clinicians was a benefit of this meeting.

States also perform and define short- and long-term followup differently within their programs. Following a

newborn after treatment and tracking their progress was also discussed at this meeting.

We've been working with the ACMG Newborn Screening Translational Research Network to consider common data elements that can bridge the gap between short- and long-term followup and to understand the varying databases that currently exist for immune deficiencies.

We've also worked with clinical experts in establishing public health surveillance case definitions so that we can facilitate consistent classification of diagnoses across Newborn Screening Programs.

During this meeting, there was also conversation led by the clinical community about harmonizing diagnostic terminology, idiopathic versus variant, classic versus typical.

Regarding education, discussion occurred around developing educational and awareness materials and campaigns for families, clinicians, patient advocacy, and support groups.

We've worked closely with the Immune Deficiency Foundation as well as the Genetic Alliance, Baby's First Test to ensure that programs know about these resources that have been developed by these and other organizations.

At this meeting, we also discussed that while SCID is not categorized as time-critical by this Committee, it is, in fact, time-sensitive and timeliness remains an important factor is positive outcomes for SCID newborns.

At the end of the SCID in-person meeting, Newborn Screening Programs had the opportunity to sit down with their state immunologists and reflect on existing issues and identify priorities for moving forward.

The following priorities on this slide were identified, covering issues as they relate to legislative barriers through the newborn screening system and through clinical treatment.

These priorities worked toward the uniform goal of improving outcomes for individuals with immunodeficiencies from birth through development.

My colleagues, Adrienne Manning from Connecticut, and Dr. Lisa Kobrynski will speak shortly about some of these considerations.

I want to end by reminding everybody that NewSTEPs in collaboration with the NBSTRN host bi-monthly webinars for SCID education. I also encourage everybody to go to newsteps.org and continue to visit the infographics and state profiles available there if you have questions about the evolving status newborn screening for SCID and for other disorders as well.

Thank you for your time.

[Applause.]

DR. JOSEPH BOCCHINI: Thank you, Sikha. I appreciate the presentation. We'll get you back up here after

the other speakers.

Okay, next we have Adrienne Manning, and Adrienne is with us by telephone. Can you hear us, Adrienne?

MS. ADRIENNE MANNING: Yeah, I can hear you fine. Can you hear me?

DR. JOSEPH BOCCHINI: Okay. We can hear you, so go right ahead.

MS. ADRIENNE MANNING: Okay, great. I just want to thank the Committee for the opportunity to speak today. I'm going to be talking about Connecticut Newborn Screening for SCID.

Next slide, please. So, a little bit about the Connecticut Newborn Screening Program. We are a legislatively mandated program, and we operate under the Connecticut General Statute 19A55. We screen about 99.9% of newborns born in the state of Connecticut, and that's about 37,200 newborns born every year for 64 different disorders. Cystic fibrosis screening is not conducted through our Newborn Screening Program at the Department of Public Health. It's conducted through UCONN and Yale Laboratories.

Next slide, please. This is a timeline for when we implemented the various testing for the different disorders. We started screening in 1964 for PKU, and our most recent disorder adrenoleukodystrophy -- X-linked adrenoleukodystrophy was added in 2016. We were mandated in 2011 to start screening

for SCID.

Next slide, please. So, our program has two components to it that overlap quite a bit. We have the laboratory end of things and then the Newborn Screening Short-term Followup and Tracking Program. The laboratory responsibilities include to receive, log in, sample quality evaluation, creating the work list, punching the samples into 96 little plates, the sample preparation, instrument maintenance and setup, sample interpretation, and then the reporting of any abnormal results to the Newborn Screening Tracking Group.

Next slide, please. So, the short-term followup and tracking responsibilities are -- part of the responsibilities include ensuring that all infants are screening for the newborn screening disorders that we screen for, reporting out abnormal results -- so either requesting a repeat newborn screening specimen or referring the infant to a Regional Diagnostic Treatment center. They maintain and report the statistics for the program, and they collaborate with a number of different individuals from the hospital and Birthing Center staff all the way to Diagnostic Treatment Center staff, primary care providers, and parents.

Next slide, please. So, the challenges for implementation of a molecular screening test in a Newborn Screening Program really come down to three basic components of

funding, staffing, and space. And, I'm going to talk about how we overcame some of those barriers for starting screening for SCID.

Next slide, please. This is a timeline for newborn screening for SCID in Connecticut. In 2008 at a National level, grants were awarded to two laboratories for SCID testing, as Sikha mentioned earlier, Massachusetts and Wisconsin in 2008. Our program was going through some pretty hard times. We dropped from 12 laboratory staff in 2006 and in 2007 to 8 laboratory staff. We had a financial crisis and budget cuts, and union concession, but there was still an interest for screening for SCID. And, that interest increased in 2009, and we started gathering information from the states that we knew were screening for SCID and from the CDC -- so, Massachusetts, Wisconsin, and CDC. And, we began to look at the methods that were out there.

In 2010, we had some training opportunities arise. In February, we were able to go to the CDC and observe that method. In April, we went to the Newborn Screening Program in Massachusetts, and observed that method. And, in May, we went to Wisconsin -- to the Wisconsin Newborn Screening Program to observe that method. And, we made an attempt in April of 2010 to acquire funds for implementing newborn screening for SCID, but there were no funds available.

Next slide, please. We also had an Advocacy Group -

- the Jeffrey Modell Foundation -- that was quite active in the state encouraging us to start screening for SCID. They sent letters to the Governor at the time. They sent letters to the laboratory staff and management. They sent letters to me. They did radio interviews. And, our lack of starting testing screening wasn't because we didn't want to test for SCID. It was that we didn't have the means to test for SCID.

So, next slide, please. So, moving forward, in 2010, SCID was added to the RUSP. In Connecticut, things were getting worse. Mid 2010 to 2011, we were now down to 6 laboratory staff. And, in 2011 a January Senate Bill 543, an Act Providing Newborn Screening for Severe Combined Immunodeficiency Disease was proposed. It passed in July with a mandated start of October 1st, 2011. They didn't give us a whole lot of time.

So, we started choosing the method. At that time, we chose the CDC's in situ method and started putting in the equipment requisitions for what we needed in July and started some method development in July as well. In August, we went down to the CDC for the preparation of the testing calibrator and control reference materials, and we began the validation in October.

So, all infants born as of October 1st, 2011 have been screened for SCID, and our official start date was January 1st, 2012.

Next slide, please. Though we chose the CDC in situ method for the three reasons that we had to go by -- and that's funding, staffing, and space -- so, the cost of the test is relatively inexpensive compared to some of the other methods. It's about $80,000 in instrumentation costs, about $10,000 in ancillary costs. We made our own QC Reference Materials at the CDC, so we didn't have to pay for that. For staffing, this method really doesn't require a lot of staffing, and it doesn't require a lot of specialized staffing because -- as I said before -- we only had 6 newborn screening staff, and we had no staff that were familiar with current molecular biology or PCR methodologies available to us.

We had a Master student intern that was available through UCONN that was going to come in and help us with the implementation of the screening method, but, other than that, we were really on our own. And, this method, though, doesn't require DNA extraction, so it's -- it's a little bit of an easier method.

For space, this method requires minimal space. As I said, there's no DNA extraction required. So, less space is needed. And, that's a good thing. But, we didn't have any space at all within the Newborn Screening Laboratory, so we needed to be creative. Initially, space was provided in another laboratory next door -- the Serology Laboratory. They emptied out a storage closet and converted it to a very small

sample preparation area. We put a dead air box in there for the preparation of our primers and probes and Master mix, and this area contained all of our pre-PCR steps and equipment. And, then we were given about 4 feet of benchtop space in the Serology Laboratory for our strategy and PCR equipment for the analysis. And, we were also able to borrow some equipment from another laboratory to increase the amount of samples that we could analyze for the validation at one time.

Next slide, please. So, the CDC in situ method that we use is an 8-point dried blood spot, B-TRECs calibration curve. It's prepared using T-lymphocyte depleted blood with aliquots of a human Epstein-Barr virus transformed B cell line that contains a single copy of Trek per cell. So, you get a nominal concentration of TRECs copies per microliter because we're adding a known number of cells to that blood.

So, our calibration curve goes from 1500 TRECs copies per microliter down to 8 TRECs copies per microliter. And, we also have quantitative and qualitative QC Reference materials. We use the Perfecta Multiplex Reaction Cocktail for the PCR amplification. We use the Qiagen purification solution 1 and DNA elution solution 2 for the sample preparation, and our primers and probes we have for both TREC and our controlled DNA RNaseP, and those are listed down in the right-hand corner table of the slide.

Next slide, please. So, a little bit about the

method. It's very easy. We punch 2-millimeter dried blood spot samples into PCR tubes or PCR plates. We add 125 microliters of the DNA purification solution S1, shake for 15 minutes at room temperature, and remove that S1 solution and discard it. Then, to the washed blood spots, we add 125 microliters of the DNA elution solution S2. Shake for 5 minutes at room temperature.

Next slide, please. And, then we remove and discard the wash buffer S2 and add 15 microliters of the qPCR Master Mix to the samples. We seal the plates. We put them on the strategy and MX3000 PE instruments and run them with the method that's listed there on the slide. It takes about 2 hours. And, then we analyze the qPCR data. We check the QC results and report out the newborn screening results.

Next slide, please. So, as I said, we had an intern from UCONN that assisted with the method validation due to our staffing shortages. And, we also had -- we set up before we started doing patient samples -- sample analysis -- a meeting with our clinical immunologist, which at the start of this, we had no idea who that would be. But, we spoke to the CDC and Dr. Lisa Kobrynski, and she pointed us in the direction of an immunologist within the State of Connecticut that could help us with this launch of our method.

We met with the immunologist to talk about guidelines for followup for possible true abnormal findings

during the validation and to set a lower limit action level for TREC recovery where we would refer the infant for flow cytometry.

Our patient sample population started after accuracy and precision studies were done. We used samples that were received between October 3rd, 2011 and November 15th, 2011. So, it's more than 4,400 samples that we used. We also had the New England Newborn Screening Program in Massachusetts assist us with a second analysis of anything that might be potentially abnormal because they have a very well-established and validated method, and we had guidance through Massachusetts, the CDC, and the Wisconsin Newborn Screening Program during the validation process and afterward.

Next slide, please. So, I'm not going to go through this slide in great detail, but these are some of our results from the validation. We analyzed 4,457 samples for our validation. We initially set the cutoff very high so that -- we didn't know where abnormal would fall, and we didn't want to miss anybody. So, we set our cutoff for all gestational ages at 55 TREC copies per microliter. And, then our initial post-validation cutoffs we broke down into full-term infants, infants greater than or equal to 37 weeks gestation, we had a cutoff of 40 TREC copies per microliter. And, for our preemie infants or those born at less than 37 weeks gestation, we had a cutoff of 25. And, then we further refined it and dropped it a

little bit for the full-term infants and kept it where it is for the pre-term infants for our cutoffs. So, those are our current cutoffs there at the bottom of the table.

We had 5 full-term infant samples that we sent to Massachusetts for analysis during the validation of our patient population; 4 of them came back normal, and 1 of them confirmed as a SCID during the validation.

Next slide, please. So, this is our current testing information or algorithm. I'm not going to go through this in great detail either, but we do set cutoffs for full-term and pre-term infants as well as the control DNA for whether or not the sample results are valid. We have a lower limit cutoff of less than 10 for either preemie or full-term infants -- 10 copies per microliter for TREC. If less than 10, those infants get referred to flow cytometry. If we don't get any amplification -- same thing. They get referred to the Diagnostic Treatment Center for flow cytometry.

Next slide, please. These are some of the results from what we've obtained since -- between 2011 and 2017. We've analyzed about 221,554 infants with this method. We have 3 confirmed SCID patients. We have some DiGeorge infants that have been identified, and a lot of T-cell lymphopenia, and a lot of those are due to prematurity.

So, at the time of our launch, our NICU algorithm was produced by the immunologist in the state to give to the

NICU physicians to sort of guide them for what to do with the results that we were sending them for these really tiny babies.

Next slide, please. So, as I said, we have three confirmed SCID infants. They are on this slide here. They are all doing -- they've all been transplanted. They're doing great. We also had the opportunity to participate in a publication in JAMA with Dr. Jennifer Puck, Newborn Screening for Severe Combined Immunodeficiency in 11 Screening Programs in the United States, which was pretty neat as well.

Next slide, please. So, everything was going along fine until mid-2014 when we started having problems with our assay. And, the graph on the left-hand side of the screen shows you what the amplification plots really should look like -- everything should be closely clustered as it goes through the amplification process, and the right-hand side of the slide shows you what we were seeing -- so, very dispersed, and we were unsure what was going on.

Next slide, please. So, we were multiple-plate analysis failures. We were 14 days of sample analysis backlog. It was very frustrating. We contacted and collaborated with the CDC Newborn Screening and Molecular Biology Program. We called Dr. Francis Lee and Jennifer Taylor was there at the time and Golriz as well, and we went through troubleshooting and eliminating potential causes of what we were seeing. So, we eliminated all the things on the right-hand side of the

slide in gray. And, they actually came out to the laboratory and sent equipment up to the laboratory too. And, we found that the culprit was actually a shaker -- a plate shaker that we had been using for 3 years day in and day out. It wasn't especially a high-quality shaker, but it was doing the job, we though. But, then it stopped doing the job that it was supposed to do, and it was an easy fix. We bought new shakers that have worked really well. So, we solved the problem, we caught up with our backlog, and it went pretty quickly.

Next slide, please. We further improved our SCID Newborn Screening Program in Connecticut by moving to a new laboratory space in 2012. So, we're not operating out of a storage closet anymore. We were able to purchase and also got extra additional instrumentation from other laboratories that stopped using the platforms that we currently are using, and we also were able to hire additional staff.

And, then in December of 2014, we had the Molecular Assessment Program come in and look at our program, and it was really a great visit and allowed us to reconfigure the laboratory SCID testing area as well as the other molecular areas for our program. And, it helped us refine what we were doing, which is always helpful.

So, in summary, Connecticut SCID Newborn Screening launch was successful; however, it wasn't without challenges. So -- you know -- now for the method choice in 2011, there were

limited choices and there were no commercial methods available. The choice was between DNA extraction methods or in situ method.

Currently, both commercial kits and LDTs are available for laboratories to choose from, so there are more choices to allow laboratories to choose between an FDA-approved kit or LDTs based on their technical expertise or convenience or any other parameters that they take into account.

In 2011, Connecticut had no expertise with PCR, so we chose the least complicated method, and it's worked really, really well for us.

For staffing, we didn't have any experience with PCR methods, but there's a lot of support and help that was available and given by other newborn screening laboratories, in particular Massachusetts and Wisconsin, and the CDC was there to assist us for the start of SCID testing and continuing with that.

We chose a method that was easier and required very little time to complete, so that also helped.

With space, it was necessary to be creative and innovative to identify and set up the minimal amount of space for the pre-PCR and post-PCR areas for carrying out this procedure, and that was an interesting time.

And, then for funding. For the types of assays that are now available, the commercial kits or LDTs, LDTs are

probably generally still less expensive, and the sharing of equipment with another laboratory could reduce the initial amount of money that's needed to start SCID testing.

Next slide, please. I just want to acknowledge all the people that helped us during the launch and have helped us since. The Connecticut Newborn Screening Program is a wonderful group. They're hard workers, and I'm proud to be a part of them -- our Yale immunologist past and present, our CCMC immunologist, the Molecular Assessment Program, Suzanne Cortavato [phonetic], CDC Molecular Quality Improvement Program and Christopher Green was just wonderful. Rachel Lee from Texas has helped us a great deal. Tim Davis from Washington has helped us a great deal. Gui Su [phonetic] from APHL has been just great. The CDC Newborn Screening at Molecular Biology Branch led by Dr. Carla Cuthbert and Bob Vo, Francis, Golriz, and Jennifer who is now at RTI -- they're just a great group. The New England Newborn Screening Program really has helped us with SCID and given us ideas for other molecular-types of testing that we can do as well as the Wisconsin Newborn Screening Program. They've also -- Dr. Mei Baker has given us a lot of ideas. And, I want to thank our University of Connecticut intern.

Next slide, please. Thank you.

[Applause.]

DR. JOSEPH BOCCHINI: Thank you, Adrienne, very much

for that presentation. We're now turning to the next presentation and we'll get the slides up for Dr. Kobrynski. Lisa, your slides are up. Okay. We can hear you. So, go right ahead when you're ready. Thank you.

DR. LISA KOBRYNSKI: So, I appreciate the opportunity to speak to the Advisory Committee. And, I'm sort of an unusual person in this field in that I am a clinician. I treat patients with severe combined immune deficiency, but I also have a Master's in Public Health, and I have inhabited part of the public health world for a good bit now. I work with the Newborn Screening branch at the CDC as well. So, I'm coming to you to talk a little bit about the clinical impact of SCID, realizing that a lot of this stuff was sort of surmised at the onset and really sort of the push for even doing screening for SCID came out of this publication by [inaudible] in the Newborn Screening Translational Research Network.

Can you hit next slide, please, so you can get up the two graphs. And, this publication, which was published in 2014 looked at this database to look at the outcome of children who had severe combined immune deficiency and what happened to them after transplant. And, this was a multicentered group of centers who reported their outcomes data and collected data on the age at transplant, the complications, as well as the types of transplants that were done. And, what was the most striking finding from this paper, really, was the fact that if you were

translating a child when they were quite young -- meaning less than 3-1/2 months of age at this study -- 94% survived at 5 years, which was a very marked improvement. But, what was also equally interesting was the fact that even if you were over 3-1/2 months of age at the time of transplant, if you had had no infections prior transplant -- so, in other words, you were asymptomatic before you went to transplant -- you did almost as well. Their survival rate was about 91%. So, that really drove home the importance of early intervention and early transplant for infants with severe combined immune deficiency, and that impacted their outcomes.

And, what was important was that it wasn't just dependent on -- or it was dependent mostly on the age, and it wasn't necessarily dependent on the type of transplant. So, whether the donor was a sibling or an MSD -- which is a matched sibling -- or they were a mismatch related donor like a parent -- it was the age that really made the difference. So, you could do well regardless almost of who your donor was.

Next slide. So, the next thing was then looking at what happened to some of the states who actually did screening. And, so this was alluded to previously that there was a publication in JAMA from Dr. Puck and others from 10 states plus the Navajo Nation.

Now, the Navajo Nation is kind of unique in that they have a very high incidence of a particular type of SCID.

So, they've been screening with California since early on. And, in this publication, they reported data from the screening of over 3 million infants, so that was a very large number of infants. And, it was population-based screening because it was all the infants that were born in those states. And, a key finding from this paper was the fact that there were 52 cases of SCID that were identified and confirmed, which gave them a birth prevalence for population incidence of 1 in 58,000. And, as alluded to previously, published reports previously estimated that the birth problems or incidence of SCID at 1 in 100,000, but all of those publications were based on center reporting or individual hospitals reporting. And, so, obviously, it was not population-based. So, for the first time, we actually have a population-based measurement. And, lo and behold, the birth prevalence of SCID was actually double what we had thought. So, that was a very important message because it meant that we were missing cases of SCID. And, this increased the importance of the newborn screening.

So, consistent with findings of the Newborn Screening Translational Research or the Primary Immune Deficiency Translational Research Network and the Transplant Consortium was that survival was still consistently fairly good. So, overall, 45 out of 52 survived, but only 49 of them went to transplant, and of the 49 who went to transplant, 45 survived. And, so that gave you a survival of 92% for those who

were treated.

But, another finding of this, which was not entirely unexpected, was the number of non-SCID T-cell lymphopenias that occur. So, this TREC testing is a test that does identify low T-cells or T-cell lymphopenia. It is not confirmatory or diagnostic for SCID. So, we knew that there were other conditions that caused infants to have very low T-cells at birth, including syndromes like DiGeorge syndrome, where they have a defect in their thiamine and also some other conditions. But, there were other conditions that we identified that we had not necessarily anticipated. And, those were actually -- those conditions turned out to be pretty frequent for that 1 in 14,000 infant. And, among those, DiGeorge syndrome led the way and still tends to lead the way in terms of the most number of infants that identify with a non-SCID T-cell lymphopenia, but followed also by Trisomy 21, Trisomy 18, ataxia-telangiectasia, which is another primary immunodeficiency that results in a combined immune deficiency and generally is not diagnosed until these children are much older when they start to show signs of ataxia and they start to have the telangiectasia.

Another syndrome was identified, one which we had not known previously caused significant T-cell lymphopenia from birth, and that’s Jacobsen syndrome, and there were many others where there were just single cases, but these core groups of 5 or 6 diagnoses were ones that have been seen over and over

again. And, so these are important in the sense that these are other conditions where we possibly have a chance to intervene.

So, what we learned from this very early paper was that while the birth prevalence was much more common and that there were a lot of other conditions that we needed to consider when we were trying to do diagnostic testing.

So, next slide, please. So, this was followed up by some individual state data of a little longer duration. In Wisconsin, that was the first state to initiate newborn screening, reported on their experience from 2008 to 2011 with 5 cases of SCID identified from 207,000 -- 208,000 births, and that gives an approximate birth problem of 1 in 41,000 -- so a little bit more common than what we thought in the 11-state data. And, then they had an additional number of patients with DiGeorge syndrome. Also, they described several patients with something we call idiopathic T-cell lymphopenia. So, idiopathic T-cell lymphopenia implies an infant that is born with a T-cell count that is markedly below normal -- so, more than 2 standard deviations below normal, but without the associated infections and complications that we would typically see with severe combined immune deficiency. And we've seen that in the New York data, that they've also reported -- other states have also now reported this. And, again, the impact of this for screening programs has been on the followup end when we are doing diagnostic evaluations, and we are categorizing

infants and then ultimately deciding how to treat them, we have to be sure that we diagnose them correctly.

So, out of Wisconsin's patients, 4 out of 5 were transplanted, and the fifth one was on a PEG-ADA, which is a synthetic adenosine deaminase enzyme replacement and all were alive and well.

New York also published their experience, and they had 9 diagnosed cases of SCID out of nearly 500,000 births, and that gave them a birth problem of 1 in 54,000 patients. Again, they saw a good number of patients with idiopathic T-cell lymphopenia, and there were a variety of other syndromes that were similar to what's been seen in other states. Similar to Wisconsin data, 8 out of 9 have been transplanted, and 1 was on synthetic ADA, and all were alive and well.

And, then California, which has the lowest births per state in the Union, reported 26 cases of SCID from California alone and 6 from other states. Now, early on, California did receive samples from some other states for screening. They still received some samples from the Navajo Nation, so the population denominator is not known for this series. Nonetheless, out of the cases that were identified, 94% were alive at the time of publication.

And, one other thing that is important to note. The idea with transplantation for severe combined immune deficiency is that it's potentially curative for immune deficiency. The

exception has been -- and, this has been not really changed by screening -- but, certain types of severe combined immune deficiency -- particularly one that is inherited through the X chromosome -- the IL-2 receptor gamma chain or IL-2 RG -- results in children who may have T-cell function restored, but do not have B-cell function restored. So, in terms of long-term outcomes or clinical impact, what that means is those children are still likely to receive benefit of early transplantation and reduced infection and better outcomes from transplant; however, it has not appeared to change our ability to correct the B-cell defect in those children, and that may require further advancement in the transplantation therapies that we use now, and that's being worked on.

So, that -- when you say that transplant outcomes, all of them had T-cell reconstitution -- well, that's actually critical, because if they don't, then they basically have no correction, and they will not continue to survive, and 50% with B-cell reconstitution -- accounting for some of those patients with certain types of severe combined immune deficiency -- where there are difficulties getting good B-cell function to return.

So, an important element from the cases in California was looking at the different subtypes of severe combined immune deficiency. So, in severe combined immune deficiency, we have identified about 14 different genetic

causes for this syndrome, and all of these genetic causes result in an absence of T-cells with pretty severe combined immune dysfunction and require transplantation, but there are some subtle nuances in how you do the treatment and how you perform it, so that means that for diagnostic testing purposes, identification of the genetic defect is actually quite critical in addition to knowing that they have T-cell lymphopenia. And, what was seen in California has changed the paradigm a little bit because the X-linked SCID was previously presumed to account for half of the cases of SCID. And, what we see in their cases here is that there is almost an equal number of SCID due to IL-2 receptor gamma chain as there are due to ADA deficiency. And, as you saw from the other two states, many patients can be treated for ADA deficient SCID using a synthetic enzyme rather than transplant, and now there is a third option, which is gene therapy for adenosine deaminase deficient SCID.

So, knowing that that type of SCID is actually fairly common changes a little bit how we might treat them and may ultimately have some effect on what we presume is the cost estimate for treatment of these diseases. And, some of the other disorders like Sinclair -- which is seen very frequently in the Navajo Nation -- those children are susceptible to cancers with irradiation because they have problems with repairing DNA breaks. And, so knowing that that's the genetic

form of SCID they have -- especially as these children may get sick and people want to do chest x-rays on them -- you might actually help to prevent late malignancy by not doing that if you're aware that this is the type of genetic defect that they have.

So, this knowledge really impacts how we treat patients and can ultimately impact what their outcomes are going to be.

And, then as I said before, they identified a lot of non-SCID T-cell lymphopenias including DiGeorge and CHARGE, which caused a thymic defect and ataxia telangiectasia.

Now, within their series, they did have 1 patient that died prior to transplant, so did not make it to transplant. So, we're still not perfect at getting them to transplant before they get too sick.

So, I can speak a little bit about our experience in Georgia -- I live in Georgia and helped the state lab set up their newborn screening lab and their process. And, they use the CDC in situ PCR method as well. And, we started screening in June of 2016. We've had 3 cases identified over a period of a little over a year where we had 129,700 births. So, that would give us a birth prevalence of approximately 1 in 43,200 births, so consistent with what's seen in some of the other states. And, among those 3 kids in the SCID, we identified 1 IL-7 receptor alpha chain, 1 purine nucleoside phosphorylase

deficiency, and 1 we do not know the genetic defect.

Now, one of the things I'll say about the clinical outcomes is that there have been concerns expressed very early on in using TREC screening for SCID is that you might miss cases of adenosine deaminase deficiency or PNP deficiency because those children are capable of producing T-cells in the thymus, but the T-cells are rapidly destroyed in the periphery due to accumulation of toxic metabolites.

And, so here we see examples of several states that have many children with adenosine deaminase deficient SCID, and our state at least finding 1 PNP deficient SCID, which may help alleviate a little bit some of those concerns. And, as the other states, all 3 of our patients have been transplanted, and all are currently alive and well.

Now, we did see, as other states -- we only have seen 1 idiopathic T-cell lymphopenia. We've had several patients with issues with their thymus. We've had 2 with CHARGE syndrome with complete absence of T-cells and several DiGeorge syndrome patients, and 1 that's an unknown. He is lacking T-cells with no thymic function, but no deletion in 22Q and does not have CHARGE syndrome.

So, again, in terms of clinical impact, it means that we need to continue to remain vigilant, and the clinicians need to be aware of the conditions that they need to be looking for in these infants that come back with severe T-cell

lymphopenia.

So, Scott Grosse is there, and he can probably comment on this paper a little bit more. But, I worked on this paper with him and Yao Ding from APHL, and we wanted to look at what was the cost impact of newborn screening for severe combined immune deficiency because there were a lot of early discussions about, was this too expensive, was it worth it because this was a relatively rare condition or considered to be quite a rare condition.

And, so -- as I said in the beginning -- it was the fact that we knew that pre-symptomatic identification led to better outcomes. And, now we're there where we can actually say that we're doing it in about 46 out of 50 states, and most states do operate on a very timely fashion. So I know -- for example -- Florida -- they are expected to get that infant in to a physician within days of a critical newborn screening result. Most states aren't quite that rapid, but there are still some issues of impact in terms of identifying specialists who will assess and care for these patients because most people don't have a primary immunodeficiency specialist in their town or -- you know -- in their area.

So, this doesn't necessarily take that into account in terms of how easy it is for them to have access. But, basically looking at data that was gathered either using Public Health Data Sources or expert opinion and experience in their

own institutions, we calculated that the total cost for screening and diagnosis would be about $741,376, but then the treatment cost per infant -- for a surviving infant -- would be about $197,260 compared to a child that was picked up with SCID who had not been screened. So, the presumption there is that the way that they're picked up is with severe infections, so they're usually generally fairly sick at the time of diagnosis, often in hospital and in the intensive care unit, and there, the estimate was that the treatment cost per infant picked up late but survived is about $460,000.

If you have a child who has SCID and dies prior to transplant, again, the cost for an infant who was never screened is still higher -- it's about $84,000 compared to $27,000 for an infant picked up through screening.

So, putting this together in terms of cost effectiveness analysis -- we came up with a reduction for treatment cost with screening for about $317,000. And, that gave you net direct cost per infant diagnosed with screening of $424,000. So, although there is still a net direct cost for screening, when you put this in terms of some Public Health Data Analysis, which are the cost per life you saved. So, there are Federally accepted dollar amounts associated with the cost of a life basically. So, if you have or presume a certain amount of mortality from SCID -- which is pretty much essentially 100% for untreated SCID but still fairly high for

children who are diagnosed late and received a transplant -- the cost per life year saved was calculated at about $35,000. And, many of the published estimates consider something to be "cost effective" if the cost per life year saved is less than $50,000 or $100,000.

So, we've met that bar. Now, it still remains to be seen when we start to then go back and actually try to get actual costs of the infants who have been screened if those cost savings actually bear out. And, we realized that the treatment cost per surviving infants and those dying are based on historical data for the ones that were not screened. So, it's kind of hard to directly compare them. But, we do have those numbers based on some of the historical data that's been presented.

Next slide. So, in conclusion, basically we've learned a few things from newborn screening for SCID. We learned that it's more common than we thought, which increases our awareness of this disorder and our index of suspicion for diagnosing children, and that early diagnosis really does result in better outcomes, and that's something that -- you know -- we'll continue to follow, and it's very important for us to gather good data on the impact of these programs. But, so far, that still appears to bear out.

But, one thing -- aspect of this that has been sort of a byproduct of newborn screening for SCID has been the focus

on early detection of SCID and the need for developing these sort of referral networks and care networks that have martialed resources from multiple centers to come together to gather data on the outcome of treatment. And, of course, in clinical medicine, we always are looking at how do we best analyze the outcome of a treatment to know what's the best way to do a treatment. And, with relatively rare diseases, this is rarely possible to do in a single center. So, it does require the cooperation of multiple centers.

So, we still have some barriers that we really need to overcome in order to make that a reality. One, as I alluded to, not all states have equal access to a specialist. There are some states, like Montana or North Dakota or South Dakota, where they don't have a single clinical immunologist in their state. In fact, they don't do the transplants in their state. They send their children out to other states. So, not only is that -- may that delay access to care -- but it also is a cost factor if you have to send the child and the family to a neighboring state to have treatment.

So, there is also the issues of -- well, if your outcome is better if you have your transplant in a specialized center that are used to doing these transplants for immune-deficient patients, does that make it more cost effective to send them to a regional center rather than sending them to your local hospital that does some bone marrow transplants. And, I

think that most of the people in our clinical community would argue that you are not being responsible if you don't go to a center that has experience transplanting these infants because we do see differences in outcome, depending on the expertise of the team that's doing the transplant.

And, then the last thing is, how do we go about the data sharing. And, this was alluded to somewhat when we talked about the followup needs here. And, we've talked about these followup needs for many years among our community as being able to gather this multicenter data using central repositories for data on newborn screening, and so efforts have been made through APHL, through the Newborn Screening Translational Research Network, and NewSTEPs to help gather some of this data. But, most of that has been gathered from the point of view of the state and the newborn screening labs that traditionally have not been involved in the longer-term followup. They're really just very short-term programmatic followup. And, in order to really demonstrate the impact of this, we really have to gather long-term followup.

So, on the clinical end, the Primary Immune Deficiency Treatment Consortium, which is multi-centers that do transplants for severe combined immune deficiency and other immune deficiencies, have done very well. They're an offshoot of the main Bone Marrow Transplant Registry and focus exclusively on primary immune deficiencies, and they've

gathered a lot of information, but not all centers report to them. It's voluntary, and it is ongoing, but it's limited in its scope because it's not every single place that does a transplant.

We also have the USIDNet Registry, which is a group of clinical centers -- not necessarily transplants but just clinical centers -- that report on their immune-deficient patients, and they've been attempting to gather data on the idiopathic T-cell lymphopenia patients so we can get a better idea of what happens to those patients, what's the best way to manage those patients. And, again, they suffer from the limitations that it's voluntary -- that one just has to submit cases to that database. And, unfortunately, we don't do a great job in this country because there's no incentive to do so, and it's very difficult for many clinicians to submit this data on a timely manner or on a repetitive manner. So, it's still a bit limited, but it is a step forward in terms of us being able to gather information about the clinical impact.

And, I believe that's all I have. Next slide. Thank you very much.

DR. JOSEPH BOCCHINI: Thank you very much for your presentation.

[Applause.]

DR. JOSEPH BOCCHINI: Let's bring Sikha back up to the microphone, and leave the phones open for our two outside

speakers. And, these presentations are now open for questions, comments, discussion. Scott?

DR. SCOTT GROSSE: Scott Grosse. Could you back up two slides, please? Yes, thank you. I just wanted -- first, I wanted to clarify -- this study was done in collaboration with Washington State Department of Health and APHL, which funded the study. And, John Thompson created the original spreadsheet model, which was adapted in this article. But, Lisa gave a great summary of the study, but the last footnote is not correct. The benefit cost ratio was the function of the assumed willingness to pay to avert premature death. For 9 million dollars -- if you assume preventing a death is worth -- society is going to spend 9 million dollars -- benefit-cost ratio is 5.3. If you assumed willingness to pay 4.5 million dollars, it was 2.3 benefit-cost ratio. 9 million dollars is the current figure that is used -- 9 to 10 million dollars by US Regulatory Agencies such as Environmental Protection and Food Safety. It is also used in Washington now. And, by using a benefit-cost ratio, you can put public health on a level playing field with other programs. The benefit-cost ratio is substantially greater than the cost-effectiveness ratio. The equivalent dollar value of preventing a death otherwise would be much lower than 9 million dollars if you used cost-effectiveness ratios with standard thresholds. So, this was -- in Washington State,

Newborn screening is considered a regulation, and the state requires the health department to prepare a cost-benefit analysis for that -- for adding a condition, which is why this was done that way. Thank you.

DR. SCOTT SHONE: Scott Shone. Sikha, I have a question for you. For the states that are still not screening, what are the barriers, what are the plans? Are you aware of how they can be -- I think it's red as well?

MS. SIKHA SINGH: That's a great question. So, one of those five states is in fact one of the APHL SCID awardees, and we're closely tracking their progress. They have -- they had to undergo some renovations within their lab space to accommodate for the SCID screen, and they also had some fee-increase related activities that they had to support, and now they're undergoing pilot -- well, validation and then pilot testing -- so they're almost there. But, the other labs also have similar challenges that they're encountering. They're working closely with the Immune Deficiency Foundation to address some of those issues -- but, mostly either legislative barriers or laboratory-specific.

DR. SCOTT SHONE: So -- I mean -- it's been 7 years. So, I guess the question I would have is -- you know -- they're unfortunately having to begin that part -- what you just said -- are the common barriers and challenges that we saw that you presented, but also are listed on every new disorder that comes

up on the Committee. So, the question is what's the -- what lessons can we learn, and what can the Committee learn in terms of what took them, unfortunately, so long to get to the point where they are right now, which several states started as soon as it was on the RUSP or within 2 years. So, were there unique challenges within the state? Can you comment on that?

MS. SIKHA SINGH: I can comment broadly. I can't speak to the specific states. I would really rather they speak to their specific problems. But, as noted with SCID, there have been some unique challenges related to how to perform this screen. That's not uncommon. We've seen that with the newest disorders added while most of them are tandem mass spec disorders. Then, there is a paradigm shift with followup, for instance. And, there are a variety of considerations that were different from all the other disorders that were previously on the RUSP. So, there aren't really economies of scale. What we've seen recently, adding a disorder isn't trivial. Like I said, lessons learned -- definitely. We've learned a lot of lessons from the 11 SCID awardees.

How can they get there quicker? I think we'd have to talk to them.

DR. SCOTT SHONE: Okay. And, just one last question is -- I don't know -- you might not be able to answer this one, and Carla is not here -- but, I know that CDC has had an effort for SCID NGS NexGen sequencing and issued awards recently. Are

we -- is this where things are headed? I mean -- is that going to be part of the algorithms? I don't know -- maybe Lisa can comment on that in terms of, is the goal to try to expand specific SCID NGS in newborn screening, or what's the plan? What's the plan around that?

MS. SIKHA SINGH: Yeah. I don't think I can comment on that, but that reminded me of something that might be helpful to answer your previous question. There were a series of funding opportunities through the CDC through NIH -- there were a number of pilots that occurred examining a variety of mechanism to initiate screening for SCID, whether it was doing it in your own lab, developing an assay, sending it to another lab. So, that might also account for some of the differences in the amount of time that it took for states to onboard.

Universal screening for SCID regarding the CDC Sequencing Initiative -- I really can't comment on that.

DR. LISA KOBRYNSKI: This is Dr. Kobrynski. I just wanted to say that some of the early labs that adopted newborn screening for SCID did get outside funding from foundations. There were some grants that came through the CDC Foundation. Georgia received one of those. And, that helped them set up the screening. And, one particular lab in Louisiana had funding from an outside foundation and was screening, and the lost their funding and could not get funding to restart screening, and they're still not screening. So, I think the

money issues and finding sources of funding -- many states ended up depending on some outside funds to help them get started.

And, then with regard to the whole genome sequencing through newborn screening, it was primarily driven with the SCID screening in mind. So far, as far as I know, it's not being -- at least the states that have applied for funding -- they have gotten funding -- their target is the SCID condition.

DR. BETH TARINI: This is Beth Tarini. A quick question -- you may have said this -- do we know what proportion of states received Federal funding to get up and running for SCID of those -- of the ones that achieved it? The larger question I'm asking is, are we back door funding this to get it up and running such that without these grants that come up through HRSA and CDC -- we should probably sort of look at the time to sort of screening in a stratified manner, the states that didn't receive funding and the states that did, because in the absence of funding like we just heard, it's a matter of then what other inputs -- let's say the funding dries up -- not entirely impossible -- or is not available for every disorder -- that this would be the reality we're living in. Like, what is the time limit or the timeframe of getting it up and running without any Federal money coming through grants or contracts?

MS. SIKHA SINGH: Yeah, that's a great question.

So, I think we can -- that proportion -- I don't know it off the top of my head, but we do have that data, and we can look at that.

DR. BETH TARINI: I think it would be helpful for the Committee to look at as we talk about time to start, because that we are implicitly relying on Federal dollars that we don't know will be there.

DR. SCOTT SHONE: And, I also -- I think -- this is Scott Shone. I think it's also important to recognize that a state's decision to specifically not add a disorder just because, again, it's the Recommended Uniform Screening Panel, not the Mandated Uniform Screening Panel, that we should be aware of if that's the case -- if they specifically decided not to add -- to get that information as well and perhaps even why.

DR. BETH TARINI: Oh, as opposed to, I wish I could?

DR. SCOTT SHONE: Right.

DR. BETH TARINI: That's a good point.

MR. JELILI OJODU: Just to add a little bit of color -- I'm sorry -- Jelili Ojodu with APHL. So, let's see. Back to your question. I think for SCID, approximately half of the states received some Federal funding -- CDC, HRSA, NIH combined -- I actually think Wisconsin received something from CDC back in the day then. And, without those funds, implementation strategies or implementation activities would be stalled or not to the point where we have 48 states screening right now.

DR. MEI WANG BAKER: Mei Baker. A couple of questions. And, I think just previously we were talking like cutoff. I just -- we've done SCID screening for so long -- at least I do not have a good sense in terms of different states doing this -- what sensitivity and specificity -- I mean, more detail is like what is our -- the positive predictive value? Everybody said, I'm screening, I got this and this and this, but I don't know the denominator, I don't know that APHL or NewSTEPS have the data. And, also, the two speakers on the phone -- you know your states if you want to say something about that, that would be great -- the false-positive rate, and this kind of thing.

My second question is more for Lisa. Interestingly, we talk about adult-onset disease, carrier -- you know -- I think SCID has a unique situation. At least we named it as transient [inaudible] T-lymphopenias. And, really indeed you detect a low TREC and the flow said, yes, indeed, you have low. But, they really resolve on their own. And, Lisa, could you comment on that? Did you see that too?

DR. LISA KOBRYNSKI: So, with regard to the sensitivity -- with regard to the sensitivity and specificity, there is good published data on this. And, I agree, it's problem is just having a population denominator, and I think that needs to be something possibly going forward when people publish their data from this, that they actually try to give

you a sense of what it is, so you can see the positive predictive and negative predictive values. The negative predictive may be a little more difficult, because that assumes that we see a missed case. And, when we publish our cross data, we assume that -- you know -- we picked up all the cases of SCID because so far, there have not been any reports -- at least in the public domain -- that a case of SCID was missed. Although, California suggested that they had one ADA SCID that might have been missed in newborn screening.

One of the issues too is your case definition. So, APHL is working on sending out case definitions for SCID. We have -- in the clinical realm, we have case definitions, but they may not always be adhered to, and so you really have to have a uniform set of case definitions to accurately define your positive predictive and your negative predictive values.

With regard to the idiopathic T-cell lymphopenia -- so, in New York's experience, they had probably the most of them. They ended up transplanting one child, but all of the other ones -- it's not that their T-cell counts normalized -- but, they never became ill. And, the child that we picked up is now over a year of age, has still quite low CD-4 cells, but has normal function and makes normal specific antibodies, has received all their immunizations, and is on basically no medicine. So, we think that for the most part, this appears to be benign, but we need longer followup to know exactly what

happens to these children.

DR. JOSEPH BOCCHINI: Just to clarify -- are those patients ones that fall in this idiopathic T-cell lymphopenia group where they don't have a known specific genetic marker for SCID, and is that how those are selected out as being idiopathic but potentially likely to improve?

DR. MEI WANG BAKER: Yes. Actually, we just had a case. It's very profound being low. Mei Baker. And, over time -- so, I think this kind of a new change, so it's very interesting o see how this plays out because we don't want to overtreat it, right? Bone marrow transplant is no small potato.

DR. LISA KOBRYNSKI: I agree that -- you know -- we don't want to rush these children to bone marrow transplant because a lot of them don't need it.

DR. CYNTHIA POWELL: Hi. Cynthia Powell from North Carolina. Just to say that we just recently started official newborn screening for SCID. We had a pilot funded through the APHL that was extremely helpful, but our state legislature had already approved it for being added.

A couple of questions. So, in terms of troubleshooting -- I'm wondering if people are collecting data about this. We had one hospital that had a huge number of positive screens, and we found out that the nurses were collecting the dried blood spots from babies in the NICU using

heparin capillary tubes. And, also that babies on heparin for various reasons -- you know -- in the NICU -- even if they got their blood spots collected properly through a heel stick, they were still getting these positive screens. And, that went away -- well, at least for the capillary tubes -- we are able to -- you know -- get them to stop doing that. So, I'm wondering if -- you know -- that information is sort of being collected to help as states come on board with this.

And, the second thing relates to this maybe transient T-cell deficiency is that we've had -- I think -- four cases now of children with congenital heart defects -- apparently non-syndrome -- not DiGeorge syndrome or other syndromes -- who screen positive and truly did have low T-cells.

DR. MEI WANG BAKER: Mei Baker, again. Actually, interesting thing is I don't know when there is a heart condition -- do they have heart surgery? Because kids going to heart surgery have secondary because the thymus is partially or fully removed.

DR. LISA KOBRYNSKI: No, it's not because of the surgery. Sorry, this is Lisa Kobrynski. So, they -- the kids who undergo heart surgery -- depending on their heart defect -- they may go to surgery at 24 hours of age. And, so if the spot is collected after that 24-hour period, they are almost all lymphopenic. It doesn't matter whether they have DiGeorge

syndrome or thymic problem or not. It's from being placed on a pump that is leukodepleted blood, which is adult blood which is very low in TREC anyhow. So, if you collect the spot within a few days after surgery, their TREC is going to be abnormally low. And, when we are looking at kids who we know have DiGeorge, we always wait at least a week to check their lymphocyte count after surgery because of that.

The other complication is when we have kids who have abdominal surgeries or have gastroschisis where the abdominal intestines are outside the wall or if they have a complication during surgery where they nick the thoracic duct and they lose all their lymphocytes -- they are also going to show up low if the spot is collected after their surgery is done.

DR. MELISSA PARISI: Melissa Parisi. I have two questions for you. One of them revolves around this issue of the non-SCID T-cell lymphopenia group, which is pretty heterogenous. And, it's clear from the data that you showed, Lisa, that the outcomes really and that the treatment strategies and the outcomes are in many respects dependent on the underlying genetic defect. Do you have any estimate for the proportion of children who have been identified through newborn screening who have actually had a molecularly confirmed diagnosis, i.e. know the genetic cause of their T-cell lymphopenia, whether it's SCID or another form. That's my first question. Maybe I should just stop there for a moment

and see if you have any comment on that.

DR. LISA KOBRYNSKI: So, if you look at -- if you look at some individual state data, most states will have -- you know -- a case or two of SCID where we don't know the genetic defect. And, when we look at them, we -- it's been somewhere between about 5 and 10% depending on the center where they never identify genetic cause for SCID. But, SCID is a specific condition compared to idiopathic T-cell lymphopenia. So, by virtue of the name, it implies that there is no known cause, so there is no known genetic defect associated with it. And, those children don't appear -- for all intent and purposes -- to have an immune defect.

So, even though the T-cells are low, the function is normal, the ability to make antibodies is normal, they are not getting sick. So, we still need to worry a little bit more about what this is. And, even in the adult community, there is an idiopathic T-cell lymphopenia that in the early days of HIV, infection was very concerning for people because they didn't know why these patients had that. Now, some of them went on to have other conditions, but some of them did not. So, that's kind of where we are with the incidence of idiopathic CD4 lymphopenia is to see what happens to them one year, five years, and 10 years down the road. We still don't know the answer.

DR. MELISSA PARISI: So, that's helpful information.

I guess the category that I'm intrigued by is those that have a known genetic problem, but it's not SCID, but it's either DiGeorge or CHARGE or some of these other genetic syndromes. And, I'm just wondering if -- if anybody's been collecting the data, particularly since DiGeorge/22Q11 deletion syndrome is relatively common. If there are any predictive factors that allow us to know which of those children with this condition are actually being picked up by the SCID screening, and whether their outcomes are different or worse than kids who don't have T-cell lymphopenias present on the newborn, but otherwise have DiGeorge syndrome, for example.

DR. LISA KOBRYNSKI: So, there's not a good amount of data on what proportion of DiGeorge syndrome patients will get picked up with this syndrome, I agree. And, it's been one of my interests to try to actually do newborn screening for that syndrome itself. But, we know from just looking at a series of patients that about three-quarters of those patients have some T-cell defect. But, less than 1% of them actually have a complete absence of T-cells. So, that means that you're really with newborn screening for SCID with the TREC -- you're really going to pick up a very small fraction of infants who have DiGeorge syndrome.

Now, long-term -- you know -- the cardiothoracic surgeons have suggested -- some of them, I think there's at least one report -- that there are children who have DiGeorge

syndrome and have a complicated heart lesion -- usually problems with their pulmonary vessels -- who have worse outcomes, especially if they have low T-cells. But, has that been vetted in any large series? No.

So, if your T-cell counts are absent, you're in the same boat as the SCID patient that if you don't have correction, that you're going to have problems and you're likely going to die because of your immune deficiency. But, that is such a small fraction of those patients. The other ones -- even if their T-cell counts are pretty low -- do okay. So, they maybe don't pop up on a screen, but their T-cell counts are not so low that they're going to have a problem.

DR. MELISSA PARISI: Thank you.

DR. CAROL GREENE: So, I wanted to address one of the issues brought up about access, but in the meantime two other things. One is, that's the first that I've heard that a baby was -- Carol Greene, SIMD -- that a baby was transplanted for what then -- now, as we're learning more about the natural history of something -- turned out to be a benign condition, and that's kind of an interesting footnote to me, and that's one of the fears that we always have and one of the reasons we try to do -- one of the reasons the Committee tries to be as responsible as it is about vetting -- you know -- what do we have in the way of understanding of the natural history and the diagnostic procedures, and how are we set up to go. And, I

think that's something that we need to --

DR. LISA KOBRYNSKI: This is Dr. Kobrynski. Let me clarify -- that child who was transplanted probably did not have idiopathic T-cell lymphopenia, as they observed that child for almost a year, and the child was becoming ill and having issues. And, that's why the child was transplanted.

DR. CAROL GREENE: Ah, that completely changes. So, I withdraw my comment with -- yes, thank you.

Then, the issue fascinating with people still using capillary tubes is that they're not supposed to and that SCID has obviously alerted people to an inappropriate action. But, I would also say that another part of that that should be investigated is if babies are getting alerted because of an abnormal screen for SCID and the question is whether it's due to surgery, that is a fundamental flaw in the system as well because that should have been a second screen, and the first screen should have been normal because nobody goes to surgery as a baby in a NICU -- them's the rules. Baby hits the NICU, we're on the way to surgery. If there isn't a newborn screen sent first, that was a violation of standard practice. So, any postop samples should be a second sample, and there should be a first one to compare to, and that's another way that seeing what's happening in the system could be a way to investigate and go back and make sure that NICUs are doing it properly because you never know if a baby's going to get transfused in

surgery. So, every baby going to surgery is supposed to have a screen first. And, I see Mei has something, but I wanted to get to the point that I was -- had my hand up for earlier.

And, that actually allows me to say something about access that we were going to say yesterday when the issue of access came up in the context of critical results. So, we do often hear about -- and it was a beautiful conclusion -- bullet point -- access to specialists and treatment in underserved areas and developing referral networks, which is an issue. And, I do not want to make light of the access to specialist issues. There are too few specialists, and one of the critical issues is not only are there few specialists, but the funding and support for access to those specialists is being cut every year as we speak. It doesn't go up, and then it actually gets cut. And, at the same time, we know that SCID is more common than we thought is was. That means we're identifying babies earlier -- babies who would otherwise be dead. And, the babies who are now being treated and living -- they're going to be more patients for these immunologists to take care of because not only are some identified and now reach care, others who would have only be cared for for a couple of years and die are now going to be cared for for all of childhood and then all of adulthood. So, the numbers go up.

But, in terms of access, it's really more about the referral network and maintaining the funding for those

specialists, because -- and, I just counted on that speaking for the SIMD -- counted on the SIMD website -- 40 -- counting the states -- 40 states have members of the SIMD. Basically speaking, everybody who provides care for inborn errors of metabolism in this country -- pretty much everybody is a member of the SIMD.

That means 10 states don't have -- they include Wyoming, they include --

So, but we still screen, and we still get to those babies within 24 hours, and it is about a referral network, and there was a comment -- my apologies, we already talked about it -- but, yes. We are waiting on the edge of our seat. I have my pager on. I'm on call. And, I've already answered two newborn screening calls while I'm here -- well, with the help of a genetic counselor.

So, we do have access, but it does -- so, I don't want to way that access to a specialist -- there's always somebody who's a champion. There's always -- they don't -- we don't get to having it on the newborn screen unless there's somebody who can provide the care. So, there's always access, and there's always access 24/7 -- 24/7/365 to start the process. Where we're getting into trouble is the provision of support for ongoing access

MS. ANNAMARIE SAARINEN: Annamarie Saarinen. I probably should just defer to Mei because she's going to be

addressing my point. But, I was just going to chime in on the thymus removal and the CHD kids, and the NICU protocols because I don't -- I don't think they are terribly well defined, and depending on what the baby is in the NICU for, I think that's where there's a lot of variability about when a specimen is being collected and when it's not being collected. And, in the case of the critical heart lesions, I don't think there's any uniform data right now to show at what age babies are being referred to the OR. I know certainly that babies are going to the OR within the first 24 hours of life -- I just don't know what percentage of CCHDs are being referred to the OR in the first 24 hours of life, and I also know that in the United States, about 80% of the heart surgeries that are happening in the neonatal period are happening with complete or almost complete thymus removal. I know this because it was a project that I worked on with Dr. Cohelis back in the early days after my daughter's surgery because I know how actually critically important that is to the development of these children and their immune status moving forward. There's many congenital heart kids that have ongoing issues because of that.

In Europe and many other parts of the world, the standard procedure of removing the thymus has sort of gone by the wayside. They just simply don't do it anymore, so I don't know why we continue to do it in the United States, and I continue to raise the issue among the Society of Thoracic

Surgeons at their meetings.

But, that said, I just wanted to recognize that it may indeed be an issue, and it may be something worth exploring if those numbers end up being in any way substantive as it relates to SCID screening. So, that was my little tiny area of knowledge and expertise that relates to the issue.

DR. JOSEPH BOCCHINI: Mei?

DR. MEI WANG BAKER: I'm just adding on a little bit mostly to respond to Carol. The reason we learn is because we do have first screening samples. And, their TREC number is different. So, that's -- and also I can only speak of Wisconsin is because we are a small state, so we know the cardiac NICU -- we know the doctors. And, so when we have this situation, I often call and say, I really need the surgery notes. So, this kind of thing. So, we pretty much have this experience. So, very fortunately, most of the time we really know the first and the post surgery numbers. So, we have the category on our report called a previous normal. So, we don't ask them for the --

DR. CAROL GREENE: Thank you both for the clarification, and that really was the point is that if there's a state where a baby is having a false positive screen for SCID because the only sample they got was postop -- that NICU is having a problem because the protocol says as soon as you know the baby has anything out of the ordinary and before they go to

the OR, you should have the newborn screen sent. And, that baby should not have a false positive -- it should have exactly what Dr. Baker just described.

DR. LISA KOBRYNSKI: This is Dr. Kobrynski. I would say that in Georgia, we also do the same thing. So, if the child had a screen at 72 hours that was abnormal, we always look to see if there was an earlier screen that was normal. And, then if there was, we don't have to do any further followup at that point.

DR. JOSEPH BOCCHINI: Okay. I see no more questions or comments. So, I want to again thank all three presenters -- Ms. Singh, Ms. Manning, and Dr. Kobrynski for excellent presentations and certainly getting us started on a very rich discussion. So, thank you.

The final item on the agenda is new business, and this is an opportunity to bring up any additional items of business. I know we had some full discussions and kind of got behind schedule because of the strength of those discussions yesterday, and everybody may not have had the opportunity to weigh in on any specific issue. So, this is an opportunity for anyone to bring up any item of business for the Committee.

Carol, did you have a comment that you wanted to bring at this point?

DR. CAROL GREENE: Thank you for asking. I snuck it into my previous comment. But, thank you. For the record, we

just want the -- the SIMD wants to be on record as showing that we do believe that the system provides -- the system provides for 24/7/365 access to specialists when the screen is positive.

DR. JOSEPH BOCCHINI: Okay. All right. Additional -- yes? Natasha?

MS. NATASHA BONHOMME: Natasha Bonhomme, Genetic Alliance. I really appreciate all the discussion that there was yesterday about the work and timeliness. And, I hope that in the future, we'll be able to delve a little bit deeper into what were those educational efforts that were put in place on many of the charts that you saw the little box that said education, and then there was the change. And, so I hope just down the line -- maybe later in the project -- there would be an opportunity to bring those findings and those lessons learned to this Committee.

DR. JOSEPH BOCCHINI: Thank you. All right. Hearing no other comments. Scott? Last chance. He's good. Okay. All right.

Well, first I want to thank -- oh. Mei.

DR. MEI WANG BAKER: I didn't know what was a good time because last time I spoke too soon. Are you asking for proposal for new projects too or not yet?

DR. JOSEPH BOCCHINI: If you have one to bring up at this point, yes, go right ahead.

DR. MEI WANG BAKER: Okay. I think you perhaps are

not surprised because I talked to you a little bit. Also, I talked to Aaron here too. And, I think it's a wonderful opportunity when we talked about the carrier, adult-onset situation, and I think the three speakers are wonderful because putting it all into respect, but I hope we do not stop here now. And, I think we need to do more work. And, also, the education can bring over -- you have to back talk a little bit about carrier and adult onset.

And, we also talked about cross working groups who have some. So, I'm going to propose a new workgroup -- the Carrier and Adult Onset. You know -- I think these three people are very good. I think we can expand a little bit -- adding on others and I also talked to Aaron a little bit. I understand actually he has done a lot of research. He has a lot of background information, and I think we have a good grand start doing more.

Oh, can I just add a quick -- I think -- I hope this workgroup can come to some recommendations, then come into the education pieces.

DR. SCOTT SHONE: Okay, I lied. Scott Shone.

[Laughter.]

DR. SCOTT SHONE: No, because what Mei just said -- you know -- this idea of a carrier and you even said the words workgroup -- I mean -- the idea is again sort of like Beth said earlier, and I think what I added on to I hope is that -- so

around that topic of carrier -- you have education issues, you have laboratory issues, you have tech, and then we have followup issues and how to deal with them. So, again, it goes back to this cross-cutting effort. So, I don't think -- so, the idea is are we really going to pursue the idea of, all right, let's try to figure out how to break down the siloes that are infrastructurally set up for education, lab, and followup workgroups and start to think about things as topics and address them or are we going to stay with the same mantra and then just delegate this to education, and then find out, well, does the lab always pick up carriers, and then we have to wait for the next meeting to throw it to the Lab Workgroup, and then, oh wait, how is Followup going to deal with it, and then we wait until the next meeting to go to the Lab Followup Workgroup, and now we're 9 months later and we might as well have just done an evidence review.

So, I feel like -- I guess my suggestion is, I think Beth's idea of prioritization and one of them might be looking at the -- how the Committee looks at these system-wide topics is something that we should pursue going into 2018.

DR. JOSEPH BOCCHINI: So, that's a good comment, and I think that in the past, we have created specific ADHOC workgroups to identify issues or to work through specific things as you mentioned. And, that is one possibility.

And, the other thing is that I think if we

standardized the calls that we have between meetings between the Chairs of each of the three workgroups, we may be able to cross fertilize what's happening in the groups and determine whether something does cross enough lines to become something that Committee addresses with an ADHOC workgroup versus being placed in a specific one of the three standing workgroups. So, that's a really good point. Yeah.

Okay. Annamarie?

MS. ANNAMARIE SAARINEN: Do the workgroups as they exist today have a defined like charter -- like this -- those three workgroups are set to expire at a certain time? Is up at the pleasure of the Chair or the Committee to determine if those become something different?

DR. JOSEPH BOCCHINI: These are permanent workgroups, and each has a set of -- a mission statement with specific priority -- with specific areas to continue to work in. And, actually at one point in time -- maybe 2010 or 12 -- I can't remember when -- but, we did kind of look at the workgroups and as a Committee determine that those three workgroups could -- should continue to exist the way they were. Now, it may be time to revisit that, but I think at this point in time, they are permanent workgroups, and they do each have a charge.

MS. ANNAMARIE SAARINEN: Well, maybe Scott, if he's willing, would be -- maybe in advance of or as part of the next

Committee meeting -- could carve out maybe like 15 minutes to put a visualization up there of how these workgroups can better -- you know -- I'm not saying ADHOC ideas isn't the right pathway -- but, maybe we can flush out a few different ideas or how we do break down those siloes, because I really, really agree that these are -- everything that each of them talks about touches the others. And, for that to be bubbling to the surface when we all give our reports on the last day of this Committee meeting every session, I think it makes it difficult to feel like there is actionable integration happening before we meet again three months later.

And, I also am not going to make a motion on this, but if anybody doesn't make roll call in the morning that wants to bring like chocolates the next time as their penalty, that I would advocate for that because it might be a deterrent.

[Laughter.]

DR. JOSEPH BOCCHINI: All right. So, Kellie, and then Carol.

DR. KELLIE KELM: Kellie Kelm. I just wanted to add on -- we've had a question and we were talking about it yesterday. Where does short-term followup fall? Does it actually belong in any of the three? Maybe it's just not clear to us if it actually does have a place that it lives.

DR. JOSEPH BOCCHINI: Carol?

DR. CAROL GREENE: So, thank you. Carol Greene,

SIMD. And, I do -- I was around when the original sub-committees that then turned into workgroups were made, and short-term followup was in the Lab. And, that's part of the timeliness as well. So, it's been in the Lab. That doesn't mean it has to stay there -- but, that's the history as I recall it.

The one thing I would say -- and, I'm very glad that I'm not on the Committee and I'm not staff, so that I have to make this decision because I don't believe that's there one right or wrong answer -- but, again, historically the reason for the -- my recollection -- the reason for the standing Committees is that when we do things -- the whole Committee is large. And, when we do things in response to what bubbles up, what people bring -- then we get back to that issue that Dr. Tarini was talking about earlier that we're often reactive. And, way back a long time ago -- and the concept has held -- it was thought by the Committee that there were three major areas that needed some ongoing attention more broadly and that the idea of sub-committee, then workgroup could bring in people who are not on the Committee.

And, no matter what way, and I -- you know -- have been in medicine for 35 years and I teach a lot -- and, no matter what way you cut things, there's always a different way to cut them. So, you can do -- you know -- one person's cross cutting is another person's silo.

So, if you take it disease by disease, then all of a sudden somebody is going to say, but, we've lost track of the long-term followup. So, the combination of things that -- trying to make things work together, but also the combination of doing things that are standing and cross cutting -- the standing helps to bring things to the Committee.

So, I'm just making an observation. Again, I'm deeply grateful I don't have to participate in the decision, but I do observe over the history that -- you know -- when you do things that are cross cutting, you're creating different silos, basically. Because any way you cut it, it's going to be cut, and there's another way to look at it.

DR. JOSEPH BOCCHINI: Thank you.

So, with that comment, we're going to adjourn the meeting. I want to thank everyone for their participation. I want to thank HRSA for having things so well organized, Catharine for all the work that she did to put together the agenda and make things work so well. And, once again, I think that we had a really good strong meeting, and I look forward to seeing you all again in February. Thank you.

[Whereupon, the above-entitled matter was concluded at 2:36 p.m.]