U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

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IN-PERSON MEETING & WEBCAST

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FRIDAY
AUGUST 28, 2015

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The Committee met on the Terrace Level, 5635 Fishers Lane, Rockville, Maryland, at 9:00 a.m., Joseph A. Bocchini, Jr., Chairperson, presiding.

PRESENT

JOSEPH A. BOCCHINI, JR., M.D., Chairperson
DON BAILEY, Ph.D., M.Ed., Member
JEFFREY BOTKIN, M.D., M.P.H., Member
FRED LOREY, Ph.D., Member
STEPHEN MCDONOUGH, M.D., Member
DIETRICH MATERN, M.D., Ph.D., Member
ALEXIS THOMPSON, M.D., Member
CATHERINE A.L. WICKLUND, M.S., C.G.C., Member
ANDREA M. WILLIAMS, B.A., Member
COLEEN A. BOYLE, Ph.D., M.S., Centers for Disease Control and Prevention, Ex Officio Member
KELLIE B. KELM, Ph.D., Food and Drug Administration, Ex Officio Member
KAMILA B. MISTRY, Ph.D., M.P.H., Agency for Healthcare Research and Quality, Ex Officio Member
MELISSA A. PARISI, M.D., Ph.D., National Institutes of Health, Ex Officio Member

JOAN A. SCOTT, M.S., C.G.C., Health Resources and Services Administration, Ex Officio Member
TIINA URV, Ph.D., National Institutes of Health, Ex Officio Member

ALSO PRESENT

DEBI SARKAR, M.P.H., Designated Federal Official
ALEX KEMPER, M.D., M.P.H., M.S., Condition Review Workgroup, Duke Clinical Research Institute and Department of Pediatrics, Presenter
JELILI OJODU, M.P.H., Director, Newborn Screening and Genetics, Association of Public Health Laboratories, Presenter
LISA A. PROSSER, Ph.D., University of Michigan
MARCI SONTAG, Ph.D., Associate Director, NewSTEPs, Associate Professor, Colorado School of Public Health, Presenter
JOSEPH BIGGIO, American Congress of Obstetricians and Gynecologists
NATASHA BONHOMME, Genetic Alliance
FREDERICK CHEN, American Academy of Family Physicians
CAROL GREENE, Society for Inherited Metabolic Disorders
ADAM KANIS, Department of Defense
CHRISTOPHER KUS, Association of State and Territorial Health Officials*
EDWARD MCCABE, March of Dimes
SUSAN TANKSLEY, Association of Public Health Laboratories
BETH TARINI, American Academy of Pediatrics
CATE VOCKLEY, National Society of Genetic Counselors*

*-present by telephone

T-A-B-L-E O-F C-O-N-T-E-N-T-S

P-R-O-C-E-E-D-I-N-G-S

(9:04 a.m.)

CHAIRPERSON BOCCHINI: Thank you, good morning. Welcome to Day 2 of the Advisory Committee meeting. We're going to start with a roll call of the Committee members and organizational representatives. So first, the Committee members, Don Bailey?

MEMBER BAILEY: Here.

CHAIRPERSON BOCCHINI: I'm here. Jeff Botkin?

MEMBER BOTKIN: Here.

CHAIRPERSON BOCCHINI: Coleen Boyle?

MEMBER BOYLE: I'm here.

CHAIRPERSON BOCCHINI: Melissa Parisi?

MEMBER PARISI: Here.

CHAIRPERSON BOCCHINI: Kellie Kelm?

MEMBER KELM: Here.

CHAIRPERSON BOCCHINI: Fred Lorey is yet to arrive. Dieter Matern?

MEMBER MATERN: Here.

CHAIRPERSON BOCCHINI: Steve McDonough?

MEMBER MCDONOUGH: Here.

CHAIRPERSON BOCCHINI: Kamila Mistry?

MEMBER MISTRY: Here.

CHAIRPERSON BOCCHINI: Joan Scott?

MEMBER SCOTT: Here.

CHAIRPERSON BOCCHINI: Alexis Thompson?

MEMBER THOMPSON: Here.

CHAIRPERSON BOCCHINI: Catherine Wicklund?

MEMBER WICKLUND: Here.

CHAIRPERSON BOCCHINI: Andrea Williams?

MEMBER WILLIAMS: Here.

CHAIRPERSON BOCCHINI: And Debi Sarkar?

MS. SARKAR: Here.

CHAIRPERSON BOCCHINI: And then the organizational representatives, Freddie Chen?

DR. CHEN: Here.

CHAIRPERSON BOCCHINI: Beth Tarini?

DR. TARINI: Here.

CHAIRPERSON BOCCHINI: Bronson -- Joseph Biggio?

DR. BIGGIO: Here.

CHAIRPERSON BOCCHINI: The Association of Public Health Laboratories, Susan Tanksley?

DR. TANKSLEY: Here.

CHAIRPERSON BOCCHINI: Chris Kus on the telephone?

DR. KUS: Here.

CHAIRPERSON BOCCHINI: Thank you, Chris. Adam Kanis on the telephone?

DR. KANIS: Here.

CHAIRPERSON BOCCHINI: Natasha Bonhomme?

MS. BONHOMME: Here.

CHAIRPERSON BOCCHINI: Ed McCabe?

DR. MCCABE: Here.

CHAIRPERSON BOCCHINI: Cate Walsh Vockley is on the phone today.

MS. VOCKLEY: Hello, here.

CHAIRPERSON BOCCHINI: Okay, thank you. And Carol Greene, where are you at? Okay. I want to thank you all for attending the second day of the meeting.

We do have a number of important items for discussion today, but we're going to start today with a presentation of, by APHL, concerning updates on implementation of screening for severe combined immunodeficiency, congenital -- critical congenital heart disease and Pompe disease.

And to do that, we have two people who you saw yesterday, Jelili Ojodu, Director of Newborn Screening and Genetics at the Association of Public Health Laboratories.

Jelili has worked in newborn screening and genetics for the past decade with significant experience in strengthening public and private partnerships. He holds a Master of Public Health in Maternal and Child Health and a Bachelor of Science in Biological Sciences.

You also met Marci Sontag yesterday.

She serves as Associate Director of NewSTEPs and Assistant Professor of Epidemiology in the Colorado School of Public Health. So I'll welcome to you both back to the microphone, and let you get started.

MR. OJODU: Thank you, Dr. Bocchini. Good morning, everyone. Dr. Sontag and I will be going through some slides here, giving updates on the last three conditions that had been added to the Recommended Uniform Screening Panel, severe combined immunodeficiency, CCHD and Pompe.

We'll spend a good amount of time on the first two conditions, and being that Pompe was just added, we'll also dedicate some time towards that and have some closing thoughts at the end of this presentation. We appreciate the opportunity to present it to you all.

We can hear you, actually. You may want to mute your phones, for the folks that are, is it -- oh, Debi's got it? Thank you, Debi.

Acknowledgment slides, always important. This is funded through a cooperative

agreement by HRSA. And APHL's vision is there. We love public health laboratories and we support public health systems.

So, I'm going to start off with SCID, and then Marci, CCHD, and then I'll come back with Pompe and both of us will conclude with our final thoughts.

SCID was, and continues to be, a major deal, a big deal in newborn screening programs, for a number of reasons. The addition of SCID to the Recommended Uniform Screening Panel in 2010, it was the first condition that was added to the RUSP since after the first 29 were added in 2005.

I noted earlier, yesterday, that the ACMG/HRSA report in 2005 added 29 conditions. It took five years to add another condition, and that condition was severe combined immunodeficiency. That wasn't the only reason why SCID was a big deal.

And where is Dr. McDonough? He said it best yesterday, he said SCID, and the addition of SCID, was a model, it's a model for a number of reasons, at least amount in, and then I think, for

a number of folks in newborn screenings programs.

You know, it was an opportunity to demonstrate and show that state public health programs can actually bring molecular capabilities. They did it with cystic fibrosis, but it wasn't a first year of screening.

SCID was actually the first major impetus to actually bring molecular testing to newborn screening programs, and it was nicely demonstrated by the folks in Wisconsin. They brought it on, with the help of a number of folks, certainly the Jeffrey Modell Foundation, the Medical School of Wisconsin.

The Centers for Disease Control and Prevention funded the first newborn screening program to bring on SCID in 2008. And I just wanted to point out some, the foundation for SCID, at least, as we moved forward then.

Papers from Jennifer Puck, Mei Baker, and Anne Comeau, that pretty much moved us in the direction of screening or publishing screening for severe combined immunodeficiency.

So, the process of adding SCID was also a first for a number of reasons. It was the first time that we developed, this committee developed the evidence base and the criteria for how a new condition will be added to the RUSP.

And, you know, for folks that lived, back then, through that whole process, you'll remember that SCID came up for review to this committee with one state that was screening for SCID, the evidence that they screened approximately 70,000 babies over a year in 2008.

And this committee said, in a nutshell, paraphrasing, that there was not enough data to add SCID at that time. They also recommended -- at that point we thought that SCID, the incidence of SCID was 1 in 100,000, that there should be more population-based pilot studies for these new conditions, and recommended funding as well.

A year and a half later or so, it was brought back and added. At that point, a number of things had happened. There were other states that were bringing on SCID, through a number of

different funding mechanisms, especially the NICHD and NIH funding of New York and California.

Bringing those two large populations to add to the number of babies screened certainly made a difference, provided us with the necessary data that ultimately led to this committee adding SCID, and the Secretary of Health back then adding SCID. So SCID was added in 2010, February, approximately five years ago.

Challenges. So, we -- and another major big deal about SCID is that there has been unprecedented, not only support, collaboration, but funding streams, not only from private organizations and institutions and advocacy groups but also federal entities.

Every one of them, whether it's CDC, NIH or HRSA, have provided substantive funds to be able to move SCID forward to where we are right now. But there are still challenges. You'll see some slides that I'll present later on where we are with, you know, the state of the state of SCIDS as of today, and what we project for 2016.

The authority to screen is still a major issue. You know, states still need that authority to screen. That authority then leads to, you know, appropriations of funds and other kinds of activities, you know, through a legislative mandate.

You know, there are other priorities that come into play when you're talking about state uniform screening programs or public health programs in general, that, you know, cause states not to be able to bring on SCID.

Funding. We heard a lot about that yesterday. I mentioned the laboratory activities and training opportunities yesterday but, you know, that still continues to be an issue, used to be, you know, bringing on molecular capabilities in states is still and issue, although there has been a good amount of effort by the CDC in training technical assistants, providing molecular workshops, molecular assessment programs to at least 15 states, to address these challenges.

Availability of clinical networks,

that's always, you know, this is something that's new for us. And, you know, even five years out, making sure that we build on other networks to be able to provide to these state programs, the clinical networks, immunologists and the availability of those in developing those relationships is still key.

And then, education, I can't talk enough about that, but throughout the whole newborn screening systems, we see these as major challenges for those states that are not screening for SCID right now.

This is the current state, or status of SCID, severe combined immunodeficiency screening, in the U.S. as of today. Please focus on the lavender, or purple colors on the screen there. Those are the states that have universal screening for SCID at the moment.

Approximately there are 33 states that are screening for SCID right now, universally screening for SCID right now. A good number of states are in the process of bringing on SCID, and

I'll document that shortly in the progression of slides that I have for UMS.

Progression. It started off with Wisconsin, 2008, on their own, with the assistance of a number of folks. Massachusetts followed closely. With the help of NICHD funding, the two largest states to bring on SCID helped tremendously in 2010, California and New York.

The two stars there represents Navajo Nation and the work that Jennifer Puck, Dr. Puck did in bringing on SCID implementation pilot studies in the Navajo population then.

And now I need to figure this out because I'm not too good with my maps. Sorry. Jennie? Oh, thank you. Oh, the lovely State of Michigan in 2011. Then other states came aboard, Texas, Colorado, Florida.

Actually, the -- this is the beginning, or the continuation of a new trend in that, in Florida, they instituted a screening for SCID, what do you call it, screening for SCID with a private entity in-state. And it allowed them to quickly

bring on SCID testing in 2012. Same thing kind of occurred in California. Lab-in-a-lab, thank you.

In 2013, Nebraska, Kansas, the lovely State of Minnesota and Connecticut also brought on SCID. And this is 2014, approximately half of the states had brought on SCID testing. And right now, 33 states universally screen for SCID, which represents approximately 71 percent of the number of babies born in the United States.

So this is what we envision, we are forecasting for the state of SCID newborn screening in the United States in -- by the end of 2016. There will be a number of things that have to occur for this to happen.

I noted that a number of federal entities have funded SCID testing in newborn screening. We, APHL, just received some funds from HRSA, although it was about a year ago now, to fund states to bring on SCID implementation.

And we were able to fund ten states to bring on SCID implementation, one state to actually bring on the molecular capabilities for severe

combined immunodeficiency, and then one entity to assist states in the implementation strategies of SCID, and I'll talk about that a little bit later.

But this is what we forecast to be the future, the immediate future, at least, by the end of 2016, the state of SCID testing. Yes?

MEMBER MATERN: Dieter Matern. In your current slide for 2015 you show that all of the states that are gray here are considering, except for Vermont, which is just not saying, not screening. What's the problem with Vermont where they get screened through Massachusetts?

MR. OJODU: Thank you. That's a good question. Is Vermont screening for -- do they have universal screening for SCID? I'm looking back there. No. So even though Massachusetts, their contract lab screens for SCID -- please? Make sure the microphone is on. Thank you.

DR. COMEAU: I went the wrong way.

MR. OJODU: Oh no, you're good.

DR. COMEAU: Okay. So actually, since we had our CDC award and began screening in

Massachusetts in 2009, we offered that screening to all of our clients in the New England region. And our program, though we're regional, we don't dictate what other states screen for, so we follow what they requisition.

So this, the -- Vermont has not yet requisitioned -- I actually understand that they're planning, for 2016, to bring on SCID. But it hasn't, we haven't gotten official notification from them yet.

And the reasons that they -- oh, I'm sorry. I'm Anne Comeau from the Massachusetts Newborn Screening Program. And the reasons that any of these states have stated are similar to reasons that any state screens, and it's not for lack of laboratory services, and there are other considerations that they've brought forward that we've heard.

MR. OJODU: Thank you, Dr. Comeau.

MS. MANN AU: Jelili?

MR. OJODU: Yes.

MS. MANN AU: I just wanted --

MR. OJODU: Please state your name.

MS. MANN AU: This is Sylvia Mann Au from the Western State Genetic Services Collaborative. I just wanted to add that Alaska should be starting in January 2016. Idaho is actually starting October 2015.

MR. OJODU: Thank you. It's a dynamic map. Things are changing. Please?

DR. BAKER: Very quick, I'm Mei Baker from Wisconsin. I couldn't see the map very well I just want to add in now, we do newborn screening for Montana, and started July 1st, Montana already added SCID.

MR. OJODU: Oh. Lovely. Please, go ahead.

DR. COMEAU: Last comment.

MR. OJODU: Your name again? Anne Comeau.

DR. COMEAU: Anne Comeau, last comment. Interestingly for SCID, I found that it was often the immunologists who had the hesitation, and even with quite a lot of education. So there's

a lot of back-and-forth, a lot of education needed, and still people have their reason.

MR. OJODU: Okay. So real quickly, to round up here, it -- before Marci comes to talk about CCHD, as I said, there have been plenty of assistance by a number of entities to make sure that SCID is -- every state screens for SCID.

I've talked about the funding opportunities, whether it was from the Modell Foundation, to the CDC -- actually, right now I think CDC has provided close to -- funding for close to 20 percent of the states to bring the implementation of SCID, NIH to bring on those large states.

That funding certainly helps immensely in bringing on SCID and understanding where the SCID, at, to the point where we are now. Technical assistance by CDC, they have Francis Lee, Dr. Lee, standing by to answer anyone's question any time, any state that's bringing on SCID.

And chains, molecular chains, NIH, through funding by the NBSTRN, as you know, has

pretty much held meetings, monthly conference calls, technical assistance conference calls to be able to help states in their implementation strategies among other things.

And we started collaborating with them to be able to assist as they bring those TAs, the beginning of this year. Those calls have been very helpful.

We hosted an in-person meeting, we, the APHL, through the funding from HRSA, for the grantees, the 12 grantee states and entities that we funded through the cooperative agreement that we got from HRSA last year.

That meeting was last month, I think. And that funding opportunity allowed the states to -- the states that are still trying to bring on SCID, implementation funding, close to $150,000 for two years, so that we can get most of those states orange, on the maps that I showed you earlier.

There are plenty of resources related to SCID implementation, or just SCID in general,

on a number of websites, some of them I've noted here including NewSTEPs.

This is our -- this is the approach that we took in providing funds to the 12 entity states and organizations that we funded through the HRSA cooperative agreement.

We broke them down into four tiers, wanted to understand what were the issues related to legislation, logistics or implementation and development of those follow-up strategies and clinical networks.

We didn't want to leave education behind, so that was a main issue here, and we wanted to make sure that folks didn't redevelop the wheel.

There are a number of folks that had developed those strategies as well, and ultimately getting them down to the fourth tier here, which is, I don't know, getting full implementation of SCID in those states.

I'd be remiss if I didn't talk about the fact that FDA did approve of a kit, an assay, the first approved assay for SCID testing. And I think

a number of states are already implementing this assay as part of their screening for SCID in moving forward.

Marci did a very, very good job of providing you all with information related to NewSTEPs. We have a number of resources on our website.

But more importantly, I think it's, you know, there is -- there have been questions of where to put the, you know, where to put, you know, how to count the number of cases, surveillance, you know, of SCID and other conditions.

She talked about the fact that we have memorandum of understanding with states to collect that data. And this is available for those states that have signed, and they are already putting that into the system.

And so for us to count the different classification of SCID and other T-cell lymphopenias, it's there. Please use it.

In summary, approximately 72 percent of all newborns are screened for SCID, universally

screened for SCID, and we anticipate that by the end of 2016, about 86 percent of the babies will have SCID screening.

This is seven years out of the first stage screening for SCID, and five years out of the recommended -- the recommendation from the Secretary of Health to add SCID to the Recommended Uniform Screening Panel.

And I don't need to say to too much about the last slide here, I mean the last bullet here. I think, from all of the folks that came to the microphone, you hear that this is a dynamic issue.

All of the things, whether it's legislative mandate, authority to screen, training activities, all of these things add up to us pretty much getting everyone in the union screening for SCID at this point in time.

So I'm going to stop here and pass it on to Marci. Oh, Ms. -- all right.

MEMBER BOYLE: This is Coleen Boyle. Thank you very much for that great overview and it's, I think it's very, an appropriate opening,

relative to some of the challenges that we noted yesterday --

MR. OJODU: Yes, ma'am.

MEMBER BOYLE: -- with ALD. So thank you very much. Just a question, and -- do we have a sense of how many cases have been identified so far, through implementation of universal screening?

MR. OJODU: We actually tried to collect that information and wanted to present that prior to this. We didn't have enough time to collect that from state newborn screening programs.

I think, ultimately, if we do have the opportunity to come back and give this kind of presentation in the near future, that will be certainly part of our updates.

In quickly circuiting, next month is Newborn Screening Awareness Month, and I think Dr. Puck actually brought up a great idea during one of the last planning calls, to collect that information.

We would be able to collect that if folks provide that in our newborn screening data repository, and we hope that the states will be able to do that in the near future.

MEMBER BOYLE: Maybe just a follow-on comment. It's been a bit of my dream that we would have an annual report on newborn screening, the number of cases, you know, some specific issue highlighted, and include that somehow in an MMWR, as a -- and, you know, there's a -- those of you who are familiar with them, Morbidity and Mortality Weekly Report that CDC puts out.

There's a section on reportable conditions. And I thought it would be just wonderful if we had, maybe just once a year, sort of a, the sort of state of the states around newborn screening.

That would really be a nice way to highlight and emphasize some of these new conditions that are added. So I'd love to be able to work with someone on trying to make that happen.

DR. SONTAG: Thank you, Dr. Boyle. I think -- this is Marci Sontag. I would -- we would love to partner with you to do that, and partner with the states to make sure we have the right information to be able to report accurately.

So that's a good idea, and further, we plan to put out a report from NewSTEPs, an annual report, summarizing the data that we presented yesterday as well as the case data that is coming in.

So switching gears a little bit, we're switching to CCHD. This was the second disorder that was added the RUSP after the initial panel. And the foundation for CCHD newborn screening really came from Dr. Granelli from Sweden, who first described the technique and how we really could be doing population-based screening.

Quickly in the United States this was studied, and we realized that this would be a great way to identify newborns with critical congenital heart defects.

So, one of the critical papers came out,

Dr. Kemper was the lead, frequently called the Kemper algorithm, but really more appropriately should be called the AAP algorithm.

I think this -- Dr. Kemper was the lead for us and helped us get to where it is now, but we really, this is, this was really spearheaded by an American Academy of Pediatrics article.

And this is the place where, you know, we're looking for that algorithm for critical congenital heart defects newborn screening, or pulse oximetry screening. Many since turn to this article initially.

There have been many modifications to that algorithm since this initial article. New Jersey has made some modifications, Tennessee. There's been some changes that, listen, can we help to improve this?

Currently, Matt Oster from the CDC and Emory is taking data from across the country, analyzing it very carefully and saying, can we improve the performance of this algorithm?

And he is pulling that data together and

finalizing it, and I think we'll be having a report out in the near future, saying, here's the performance of these algorithms side by side, which is really very helpful for all us to understand how to best screen these newborns for these heart defects.

So it's an addition to the RUSP. This the letter from, or from Dr. Sebelius, Secretary Sebelius in September of 2011. You see how on here it says, "I have decided to adopt the SACHNDC's first recommendation to add CCHD to the RUSP."

Remember this, there was significant controversy about this. We weren't sure if she would adopt it or not. In September 2011, she did adopt it. There were some caveats here. We need to have further study at altitude.

We need to continue surveillance of these infants, identify, you know, develop some surveillance systems, but very exciting that we now had our first point-of-care test on this new addition to the RUSP.

We had EDHI on the first 29, and now CCHD

was added. But with that, and being a point-of-care test has brought its own unique challenges.

So those challenges, approval of legislation, that's our common theme. But the approval here is a little bit different. Many states have the authority to add a newborn screening dried blood spot test through their regular panel, through their board of health, their commissioner of health.

They might need to seek additional funding through legislative mandates, they might need to do something else, but many of them have that authority to do it other ways.

And sometimes that authority is not granted through the local legislation to do that, and many states had to go through a legislative push. There were also many advocates who were really pushing through legislation to get this added to state uniform screening panels.

So this was a different approach, I think, for newborn screening, that the American

Heart Association jumped in, the American Academy of Pediatrics and a lot of groups who said, hey, we really want to help move this forward.

This is a point of care test where, now don't control all of the testing in the laboratory, we have to think about how do we get that equipment out, who's paying for the equipment, what's that workflow in the hospital, how do they do it?

And hospitals were also hearing from the American Academy of Pediatrics recommendations and saying, oh yes, we're on this, we've got it. And some of them were implementing at the same time hospital were -- or states were mandated.

But it does take training, and it does -- as I mentioned earlier, how do you determine that best algorithm for your local implementation?

Then we have a series of special populations that, for those of you in the CCHD community, we spend a lot of time talking about these special populations.

What do you do in a NICCU? Babies are on oxygen. They're getting monitored very

carefully. Do we screen? Do we not screen? When do we screen? How do we screen? Do we repeat it? Lots of different approaches to that.

And I think many states are still modifying their approaches to what to do with those NICUs to make sure they get the appropriate screening without overburdening the system within those NICUs.

Home births? How do we make sure those home birth babies get the screening? Some legislation has not included home births within that mandate, and yet we all know that we want all babies to receive the screening no matter where they're born, so how do we ensure that that happens?

High altitude? Challenges of high altitude when you're measuring pulse oximetry, especially in the newborns with delayed transition that we know happens at high altitude. So how do we deal with that, and not a lot of babies born at that high altitude, so there's not a lot of numbers to draw from to help inform us.

And then the last special population

are those rural areas, babies that are born at long distances and in small hospitals -- long distance of, from major cities, and in small hospitals that may not have echocardiogram support. They fail to screen.

What do we do with those babies? How do we get the appropriate support for them? What's the timeliest way to do that, to make sure they get the right level of care?

And this one's so challenging we have two slides of challenges. So, we also have a data collection challenge. And what kind of data are we collecting here?

We're thinking of the data on those newborns who are identified by, or with the CCHD, and those newborns, just from their screening, they get that screening done.

How do we follow up on those babies and know that they did get the screen done, what were their values? What -- how -- what's the spectrum of information that we'd like to collect?

The first challenge, though, is the

state authority to collect data. Typically in newborn screening, the data is generated by the newborn screening program, and pushed out back out to the hospitals. Now, so we would like to collect that data, collect it in the hospitals and send it in.

Now, in EDHI, sometimes there was special legislation that was passed, special regulations that were passed specifically for EDHI. For CCHD we had to think, we need to think, how do we do this?

Some states wrote that into their legislation, that they had -- yes, the state had the authority to collect, and some didn't. So without that authority to collect, some state public health departments are actually not permitted to collect that data from the hospitals and store that.

The mechanisms to collect data, how do you guys do it here? Filling it out on a piece of paper and faxing it into the public health department? Some states are actually doing that.

Are you doing it through an electronic birth certificate?

And I'm going to talk about that in a little bit, but this is a challenge of how do you think about that? How do you conceptualize that? We need to get the hospital tie-in and buy-in to collect that data and send it in, enter that data into whatever mechanism it is.

Defining that minimum data set. I mentioned a little bit about what data we'd like to collect, the pulse oximetry values, pre- and post-ductal value, the time, they fail, do they get additional screenings? How do we do that and how much information do we want to have, locally?

Funding for surveillance, tracking those babies long term, saying yes, we've identified them, here's how many babies they are and then tracking them long term, and then quality assurance and quality control systems.

One of the benefits we have for the opportunity is partner with a birth defects registry. Many birth defects registries are

already collecting this information, and collecting quite a lot of information about these babies with congenital heart defects.

So this is a great way to partner and collect that data, and especially as we are identifying false negatives.

And as Jelili mentioned, we're constantly aware of that educational need. This a new type of screen. So of the staff at many different levels in the hospitals, staff in the public health department, how many understand what's going on with CCHD?

Our leadership and within our states, the clinicians who are caring for these babies, both of the cardiologists who care for the babies with the positive screening so they know what's happening, and have that system in place that, when somebody's going to call in to say, what do I do with this baby in rural western Kansas, what should I do, that cardiologist is prepared, as well as the PCPs, the pediatricians, so they know what's happening in PCH in screening.

And finally, the community and advocacy groups, they know where we are, how we're supporting CCHD newborn screening.

So here's the current status. I'm going to do the same type of thing that Jelili did, where I'm going to show this current status, which gives you a little more detail of where we all are.

And there's several states here, in 2015, there was a lot of progress, I think, made in the last couple of years, with CCHD screening, and that legislatively -- legislation was approved in several of these states.

So I'll show you what that looks like in that progression of slides that Jeleli, similar to what Jelili showed.

So here's the progression, 2012, when the mandate came into place. We had a handful of states screening. Let you appreciate those states here. 2013, there were many more states that were screening.

I'd like to bring up the fact that, in this time period, HRSA also funded six states to be,

to receive funds for implementation. How -- demonstrate that you can implement CCHD newborn screening in your states, develop those data systems, develop the tracking, educate people, get it out there and let's learn from them.

So we learned a lot from those six HRSA grantees. Many of them are highlighted here. As we move forward, you can see HRSA -- some of the HRSA grantees are moving into the green. In 2014, this is pretty rapidly moving forward, 2015, and this is what we anticipate by 2016.

And most of these are actually going to be added on by the end of 2015, early 2016. So this is the status as we see it, states who are reporting in to us, in 2016.

So I'm going to just go back, because this would be more fun if it was a JPEG and all that, or a fancy animation movie. So I'm just going to go back and move through this, '12, '13, '14, '15, '16.

Now the astute among you would say, well that seems like a shorter time period than what we

had for SCID, and yet there's more states screening. Why does CCHD appear to be faster than it was for SCID?

Why is that? So thank you. Jelili asked. So why is that? And I think that there actually are several reasons. There are the -- there are challenges, there are some laboratory challenges, there's funding challenges with SCID.

However, I think a difference here for CCHD is that hospitals are pushing it forward, so there was that implementation from the hospital side, and there is a wide variety of public health involvement in this.

And when I say a wide variety, there are some states who have complete data collection on every newborn with CCHD, where they're collecting every pulse oximetry value, they're monitoring, they're doing that surveillance, and they have developed that surveillance system.

But then there are many states that are represented here in green -- where there is a public health mandate -- and that's where it stands. They

have every baby screened, but no data is being collected.

So we don't have, then, that public type information to say, wow, what's happening with these babies? Are they really being screened appropriately? Is that algorithm, which is not necessary -- you have to be well educated, think about that algorithm to understand when that baby failed.

Are they appropriately applying that algorithm? Are the babies getting to the right place? Are they getting the right surgery? Are -- what's happening? And in many states, we don't know. And that's to the frustration of actually many of the states.

But the state public health departments really would like to be able to collect that data, and they're not. So developing that public health infrastructure for CCHD has been varied across the states.

Wherein SCID, SCID babies are -- and newborns are screened for SCID, and that

infrastructure isn't necessary. There's a couple of questions.

DR. TARINI: Beth Tarini, AAP. I'm not sure how this differs from the others, though, because we don't know what's happening with -- do we know what's happening with SCID cases? Do we know that they're being referred correctly? I mean --

DR. SONTAG: So we --

DR. TARINI: -- is this unique to CCHD?

DR. SONTAG: I would say the screening is unique to CCHD, and that -- the follow-up is not. So I may have over-spoken on the follow-up, but the -- we do typically know for the blood -- dried blood spot screen, but we get them to the right -- we hand them off and charge their follow-up to a provider.

That's where we, as the newborn screening traditionally say, we're ending short-term follow-up, we've handed them off to a provider. In this case, this is a little bit out of our hands. So we don't know what's happening for CCHD in many of these cases.

But more importantly, we don't know what's happening with the screen itself. Dr. McDonough?

MEMBER MCDONOUGH: McDonough, I'm family with North Dakota and the legislature passed, in 2013, a law that simply is, the health department sent a letter to hospitals saying you should screen kids, and that's it. They have no idea if it's being done.

So to say that North Dakota is fully, has a full program, I don't believe there's any basis for saying that. I mean, they have a piece of paper that got mailed and that's it. So, again, to say that babies are being screened in our state is -- I have no idea if that's happening.

DR. SONTAG: So, thank you. That's -- you're exactly making my point, that legislation is in place, or letters are in place, there are rules in place, something is in place in all of these green states, and yet we don't know what data we're getting. We just don't know what's happening with those newborns.

MEMBER BOYLE: Well I was just going to say that I thought there was a unique opportunity with CCHD, because we do have birth defects surveillance programs. Every state has one. There are varying quality. There are -- some are really good.

So I know we could take a look at, and get a better sense of how this is rolling out relative to SCID, at least to have some idea of the -- because most of these children would be picked up by even the passive surveillance programs in states, so --

DR. MCCABE: McCabe from the March of Dimes. The comments are expressing my concern, and that is, we talk about newborn screening as a system, and yet these point of care screenings have not really been incorporated into the public health newborn screening system.

And that's very concerning to me, for quality reasons, for follow-up reasons. There are all sorts of reasons, and I really think that we need to pay attention to that.

DR. GREENE: In following on, I would also ask the question, clearly it is critical that babies receive this screening. There are lots of screens that are done for babies -- bilirubins, Apgars, physical exams -- that are not part of the formal public health newborn screening system.

And just as the committee has a responsibility to look at every screen, my question is: is this telling us that we need to work harder to incorporate this into the public health newborn screening system, or is this telling us that the combination of the birth defects registry, JCAHO, AAP and clinical professional guidelines might be the right way to go for this one?

MEMBER LOREY: Yes, my comment is that I didn't feel, when this came up, that the hospital-based test belonged with the public health newborn screening programs. We run blood tests, genetic tests.

We take a lot of pride in our quality control. And I don't think a system where the data is accumulated by somebody else and then sent to the

program is an appropriate way to deal with it.

So, in California -- and I understand there are a few other states do this as well -- we moved that over to the newborn hearing screening, which is also separate. But I believe it needs to be screened. It should be in there. It should be within the -- within our purview.

But I don't think enough attention was paid at the time we were discussing it, so this might not be the appropriate place for it to be.

DR. BAKER: A quick comment is that, because the question is why CCHD got in quicker than SCID, and based on Wisconsin, it --

UNIDENTIFIED FEMALE PARTICIPANT: Please state your name, Dr. Baker.

DR. BAKER: Oh, sorry. Mei Baker from Wisconsin. And once in, based on Wisconsin experience, I want to adding on here is the time, when we have a HRSA grant to start to do this, we do the survey. Actually, the hospital already do the screening.

We have 65 percent, the hospital already

done, and the emphasis was get a better connection. So that's part, I think, can be contribute to this.

Another is that yes, I believe that Wisconsin, we utilize the newborn screening cards as the vehicle to get a screening data, yes. So it's kind of, you know, one system. I think of the, this couples in maybe for citizens, things are getting put.

DR. COMEAU: Anne Comeau from Massachusetts, and I sit on our Birth Defects Advisory Committee. And following on what Dr. Baker said, I think that the speed, you have to take into consideration that most hospitals were doing screening in their NICUs.

And so we're really talking about an expansion from NICU-based screening to universal screening. And when one is considering data for evaluation of the efficacy of the program, I think a big part that's been left out of this is the obstetric data.

All of the prenatal screening that goes forward, that gives indicators of babies at risk who

might also be found by a newborn screening, and the overlap of those data, I think, are important questions to a public health program, to know really what we need to do, where are the barriers, and who really needs the most help.

And I don't know how we begin to collect those data.

DR. SONTAG: I think we actually see from many complications that are coming out within the last couple of years, that many of the babies with the critical congenital heart defects in larger cities are being identified prenatally.

And so then our yield is very low in some of those large obstetrical centers. And maybe the biggest benefit for CCHD screening is out in the rural areas, where the moms might not have that same access.

CHAIRPERSON BOCCHINI: Dr. Biggio?

DR. BIGGIO: Joe Biggio from ACOG. It's -- what's really interesting to me is if you take these maps for CCHD and compare them to the SCID maps, because they -- like if you overlayed the two,

and really then tried to look at: what's the difference in those states?

Because when I looked at how this evolved, I saw that a lot of the -- what I typically look at is the poor resource states, adopted CCHD screening early, and they still were gray on the SCID screening up until now and to the projection of 2016, when I look at, like Alabama, the states in the South.

So why? What's the difference there? And, you know, I think there's an opportunity to learn something, that as more things get considered for the screening panels, what are the -- I mean, are there those unique barriers in those states that things like this aren't significant hurdles, but the, you know, the metabolic, the biochemical things are a much bigger hurdle.

Because it's still, you're going to have the sub-specialty access issues are still there, regardless.

DR. SONTAG: Yes; excellent point.

MEMBER BOYLE: This is Connie Boyle,

last comment. So for CCHD and other newborn health issues, we have thought about trying to unbundle the newborn -- both the newborn screening billing code as well as those other newborn preventative services that are provided, such as the vitamin K shot and all of that, so you could actually have a way of monitoring at a hospital level, whether a child was receiving this.

Right now it's all bundled together, so you can't use that. But it'd be a great metric to be able to do that. So even though these states are green -- well they were green --

DR. SONTAG: They're separate.

MEMBER BOYLE: -- you don't know how many children are actually getting screened. But if you had just a fairly simple way of doing that through the hospital codes, the billing codes, you could do it.

CHAIRPERSON BOCCHINI: Will ICD-10 change that? Or will -- was that --

MEMBER BOYLE: There are codes that exist; it's just the way the billing is done. And

those of you that are in the hospital world know that it's all bundled together under a newborn service code.

DR. TARINI: Beth Tarini, AAP. So we worked on this in the Region 4, and with my others about this, to unbundle the birth code is almost like changing the constitution, it seems. It is unlikely to be done.

You can certainly look for line items in it, but one, to unbundle that birth code is, I believe, nearly impossible. ICD-9 may change your codes, but you won't unbundle it.

And the second is, you can't -- it's, also it seems a herculean effort to increase the DRG reimbursement. If you want to say, well, if I -- from a separate issue, if I want more money, we'll just increase the DRG. It's normal newborn, is my understanding, and sick newborn.

Newborn in the NICU, then you can itemize the bill up to millions of dollars. You really cannot, it seems, do so in the well-baby situations.

CHAIRPERSON BOCCHINI: Joe?

DR. CHEN: Freddie Chen, AAFP. Both of these presentations certainly call again for the real need for updated outcomes data on both of these, so that we, you know, we are in a process measure zone right now, and an evidence-free zone, if you will, in many ways, because we don't know how actually these programs are performing. We know only about implementation.

So that's the first point. The second point is related to that, in that, you know, our discussions yesterday and ongoing around the committee around the preparedness, and laboratory preparedness as well as really sort of, we don't want that --

These stories about implementation are important, but we're hearing the, kind of the same story with every condition, and we don't want implementation to be the only reason a condition does not move forward.

So what that really calls for is a better and more critical analysis of the evidence that are

there. And I think, for both of these conditions -- I was at this table for those discussions -- we did not and continue to not have good outcomes-based data on sort of what the population-based screening looks like.

And we're in a position where we can start to look at that, but we really need to consider that critically, and not let it just be an implementation story.

DR. SONTAG: Yes. And so I'm building off of that, and how do we get information to kind of help us make those decisions? I'd like to draw your attention to an MMWR article that was written in a nice collaboration across many different organizations this last summer, really talking about how states implemented CCHD screening.

How did they add it? Was it added legislatively, added to the rules -- all of those implementation stories -- but then building from that, how do we have information on the babies who are being identified? What information is being collected?

And so, while there's much more information here, I am piloting -- for the purposes of this presentation -- that data collection piece, because I don't know that we're collecting what we necessarily need, and that's what we've been talking about in the last few minutes.

So all the states that have implemented or were in the stages of planning to implement CCHD screening, 25 had current data collection, 14 had futurem, and 13 had no plans for data collection.

Now you say, what does that data collection mean? What data are they collecting? All over the board, I'd ask you to look in the paper and you can see what states say they're going to collect, but many of them aggregate data collection only.

So from a given hospital, yes, we are collecting data, but we said, 1,000 babies were born, 12 failed, and this is what happened to those 12. And that's the level of data collection given. That doesn't really help us to improve the screening.

Many are doing pass/fails; some have O2 saturations on all the newborns. So every baby that gets screened, they're giving the oxygen saturations.

And some have it just on their failed newborns, really utilizing their birth defects registry. So we're all over the place on how -- what data and information we're getting back at the public health.

What types of mechanisms are they using to collect the data? And this is a challenge to get that data information back in, the electronic birth certificate, using the birth defects registry on those who are identified as a case.

The hospital electronic medical record, extracting data from that using many different mechanisms; the dried blood spot card, where somebody's writing that information on the card. Some states are actually using paper forms, writing information down and sending it to the health department.

And then there's some states who are

using Health Level 7 or HL-7 messaging and automatic file transfers. So all over the place on: how are we getting that information in?

There's many people who are thinking of creative solutions to this, but this is, for CCHD, if we're going to be able to answer any questions, this where our next focus has to be. We have to -- to be able to have evidence, we have to have data. Otherwise, we're kind of stuck in this implementation stage.

The other place that we get data, we -- the question we get all the time is: how many babies have been identified through CCHD in the country? Anybody know? Through CCHD screening?

I'm not going to tell you, so don't worry. I'm not going to give you any more information; I'm going to give you a way to collect it, though.

This is -- just as Jelili's put up there for SCID -- we have the repository to do this. It's a HRSA-funded repository to collect information on these newborns. There's additional information

that we collect as far as the time of collection, time of screening, time of birth, all of those things.

And then we have the seven primary screening targets that have been mentioned in many of the manuscripts, and the additional five that really are being recommended by AAP, for a total of 12 targets that people can select. Yes, this baby was identified, and here's the defect that we found.

And there's separate assistance webinars; you have this in your slides. I'm actually going to move on because we need to give time to Pompe. But there's been a lot of information that is being shared across the country.

There is a bi-monthly webinar. If you're interested in CCHD and aren't in those bimonthly webinars, please let us know, because there's great, great information, a great network of people that is coming together to share their experiences with CCHD.

And this is why we do it, for these

beautiful little babies. And this is an example of that screen happening on her -- on her hand.

So thank you very much. Thank you for the good feedback and the good conversation, and I'm going to pass it over to Jelili.

MR. OJODU: Moving along, the momentum, quickly discuss Pompe here. So Pompe was originally brought up to the Committee's attention in the form of a nomination, earlier on, I think, in 2013.

It was recommended by this committee through all of the work and evidence of the screening from one newborn screening program -- the State of Missouri -- in 2014.

And the Secretary of Health -- Secretary Burwell, the new Secretary of Health -- added and accepted the recommendation after about a year, of the, this advisories committee's recommendation to add Pompe, which was the first LSD to the Recommended Uniform Screening Panel in March of 2015.

I talked a little bit about Missouri

there. They began their state population-based pilot testing in January of 2013. And we have a little bit of numbers to Dr. Boyle's comment about, do we know -- do we have some numbers from the states that are actually screening, I guess, in that there are not that many states screening for Pompe yet. We were able to quickly call them and they were able to provide some real numbers for us.

But as I noted, the pilot in Missouri started in January of 2013. Advisory committee recommends the Pompe to RUSP in June of 2013, according to our timeline here.

And there was a little bit of back and forth between, I would assume, the Secretary of Health and agencies -- federal agencies that are working on different activities related to newborn screening -- to better understand the addition of this new condition, the first of the LSDs to the Recommended Uniform Screening Panel. But ultimately, she responded and said yes early on this year.

State of New York also started

population screening -- universal population screening -- for Pompe in October of 2014. I may actually add that this was in line with funding, or coincided with funding that they'd received from NIH to bring on pilot testing for a population screening for Pompe in the State of New York.

And it was very helpful to have that funds -- not only for the State of New York, but also two other states were funded to bring on pilot testing for Pompe.

And then we have Illinois -- that's going to be starting, or actually just started not too long ago, the screening for Pompe in June of 2015 here.

These, below there in red, are the numbers that we got from the states. I noted that New York started in 2014, October, and according to Dr. Rossini, as of August of this year, they have referred about 33 cases of additional follow-up from approximately 210,000 births in the State of New York, for Pompe.

For Missouri, they have referred,

approximately -- since 2013 -- about 107 cases for additional follow-up with the same -- approximately the same number of births.

The screening methodologies that the states use are below in question. New York, mass spec, and molecular testing. In the State of Illinois, they are also using an LC mass spec, and then planning to move forward with the -- I forget what FIA is at this point in time. Yes, please?

MEMBER MATERN: Dieter Matern. In New York, they may use molecular, but unless Michele tells me otherwise, I believe that it's not really used as part of the screen, because any baby that has a low DA activity will be reported out independent of the molecular results.

MR. OJODU: That's correct.

MEMBER MATERN: So there's another reason why they have fewer --

MR. OJODU: Oh, that's not correct. Michele's coming to the microphone.

DR. CAGGANA: No, we do the molecular, and if the baby's only pseudo-deficiency, they're

not referred.

MR. OJODU: Thank you, Michele.

MEMBER MATERN: So that explains --

MR. OJODU: And that was Michele Caggana from New York.

DR. CAGGANA: Oh sorry. Thank you.

MEMBER MATERN: This is Dieter Matern again. So that would explain, then, I assume, the difference in number of referrals in New York and Missouri.

MR. OJODU: Thank you, Dr. Matern. The State of Missouri uses a different methodology in the digital microfluidics; that has worked very well for them.

Then so you see the three different methodologies here. These are new technologies -- well no, mass spec is not new, but they -- every state needs a dedicated mass spec to be able to screen for these new LSDs, and so that's an additional cost that comes on the state.

Certainly, using digital microfluidics is something that states have not used in the past.

And I'll talk about that in my challenges there.

This is the current state of the states as it relates to Pompe screening, as of this month. Most states are red. A couple of states -- well three states -- are universally screening for Pompe right now; I mentioned them earlier.

There are a number of states that are considering Pompe as part of their uniform screening panel, and they are highlighted in blue there. And we have some oranges being considered but not yet approved yet.

So, just briefly here, I talked a little bit about the work that Missouri performed and provided to us. I think it was certainly the basis of -- it certainly helped in adding to all of the evidence-based review that this committee considered before adding Pompe to the Recommended Uniform Screening Panel.

They are screening for Pompe and a few other lysosomal storage disorders, using the digital microfluidics. And then they have a stand-alone machine, dedicated machine, that they

use for screening for Krabbe at this point in time, that's currently being validated, and in the near future, Niemann-Pick.

Wisconsin received some funds from the National Institutes of Health, NICHD, to bring on pilot for Pompe. They are looking, and a bill has been introduced to screen for six LSDs. All of them are noted there.

I think that they are working through some challenges, and they hope to be able to address some of these challenges in the near future to be able to screen for Pompe in their populations.

New York, as I noted, the funding from NIH was very helpful in bringing on Pompe in their state, and that it started off the pilot for, in several hospitals. I'm sorry. That's something completely different.

The pilot was population-based for everyone in the State of New York for Pompe. But they are, there is a current pilot testing for other LSDs that are currently going on, including Fabry, Gaucher and Neimann-Pick and MPS I.

And they are also screening, as you all know, for Krabbe and Pompe. And as we heard yesterday, they are able to multiplex on their mass spec, the screening for Pompe and Krabbe with also adrenoleukodystrophy on that same mass spec.

This is a pilot that was in Washington. This is a pilot that was done over, I think, a couple of years, a little bit over 100 samples that would be identified -- and a newborn screen dried blood spots using mass spec and I think molecular -- that has yielded very good results and is -- they're now thinking about expanding into other LSDs.

They don't currently have a mandate to screen for any of the LSDs, to my knowledge, in the State of Washington at the moment. But that's something that probably will change in the near future.

A picture of the lovely machines, the digital microfluidics assay, fluorescent assay and the mass spec that is being used. And then just the status of other states that are thinking about, that are required but not have fully implemented

screening for Pompe here -- New Jersey, Kentucky, Texas and Michigan.

And other states -- including Colorado and Ohio -- are considering the addition of Pompe at this point in time.

It seems like the addition of Pompe is something that is, should still be fresh in our minds, being that it was just added not too long ago.

Certainly, a lot of discussion the late onset of this condition and, you know, what we are picking up in newborn screening and how that affects long term follow-up and what we report out.

If I remember correctly, the cost of treatment was also a major issue then -- and it will continue to be -- for states that are bringing this on and figuring out who is going to pay.

I think the approximate cost then was about $300,000, depending on the weight of the infant, and that increases incrementally throughout the life span of the newborn.

You know, it's been, it's -- so, I'll talk about this in my next slide. We are

incrementally adding new conditions to the Recommended Uniform Screening Panel and, you know, adding to what states have already started to screen for.

And I think it just takes a while. I know Dr. Chen talked a little bit about -- you know, we're talking about the implementation story, this is unfortunately all we have to deal with at this point in time.

I agree with you that we do need to figure out how to bring more outcome studies, but the more conditions that are being added, the more that we face implementation activities and challenges, and that's what you will hear from us.

Dedicated instrumentation, LIMS system and staffing; I'm not going to add anything to that.

This was a lovely slide that was developed earlier on several years ago. I think Susan Tanksley from Texas helped in developing this. We wanted to better understand who -- oh, Michele Caggana -- Dr. Caggana from New York helped develop this slide.

We wanted to better understand how states added conditions to their Recommended Uniform Screening Panel. What are the things that have to happen after they have the authority to screen? And how long they took.

And so when we talk about the one to three years, these are the kinds of things that we're talking about that have to take place.

And for the conditions that have been added already to the RUSP, some of the states have not actually adopted or gone through all of these activities, not to talk of the training and the other kinds of needs in place there. And so it's always important to remember this, as we add conditions. I know states do.

I wanted to use this opportunity to highlight the importance of the public health impact -- the public health system impact. In the past, there have been limited data that was provided on the public health impact for CCHD -- severe combined immunodeficiency -- and we started with, a little bit with Pompe.

At the present, we are thankful for the opportunity to at least share with you all some of the public health impact for MPS-I as you heard from my presentation and yesterday, X-ALD.

And, you know, I think it's always going to be important to hear, you know, what states are going through in evaluating not only the implementation strategies, but in moving forward, the outcome measures as well, for these conditions that are added.

And I talked, you know, about the incremental adding of new conditions to the Recommended Uniform Screening Panel, you know, ultimately when we say one to three years for a new condition, and we said that for a condition that's been added a year before.

You know, I think to Dr. Botkin's point, with all of the dynamics that I talked about earlier, and Marci has alluded to, it's -- there are going to be a number of reasons why states cannot bring that condition up within one to three years because of other things that they have to deal with

in the newborn screening programs, even though the evidence is there to bring on the new condition.

Marci? Is there anything you want to add to our presentation? I think -- oh, yes please, Dr. Tarini.

DR. TARINI: Beth Tarini, AAP. You make an excellent point, Jelili, which is the challenges in bringing up the disorders to the -- to -- across states. And so we have examples here of more than three years passing and many of these conditions, or most, and still not complete uptake or where we'd like.

And the relevance and the impact that comes from the public health assessment, yesterday it seemed that the discussion centered around the fact that the feasibility is based on the fact that two states are screening.

And in some of these instances, there's been examples that there were two states screening -- maybe pilots, maybe not. And yet the feasibility of implementation does not seem -- depending on what your metric is -- to have come so

quickly so far.

So it, to some degree, raises the issue of: how does, do we as a community assess the feasibility if, having -- clearly by your data, having states implementing it, up and running -- two, for instance -- does not necessarily predict feasible uptake, even within a three-year period.

MR. OJODU: Yes?

DR. SONTAG: So I'd like -- this point was made several times yesterday, about the -- this is Marci Sontag -- about the one to three years. And slipping back to the slide, the one to three years that we're talking about is this bottom line. This is the implementation section.

So once funding is in place, and approval has been sought and the -- we're ready to go. So yes, my state says we can screen for this disorder, and I have the funding to do it; I must have the pilot studies, the implementation studies and the lab. I'm like, oh, we can do that in one to three years. We can get things running.

And there -- that process actually is,

I think, pretty efficient. The parts that aren't so efficient are the, getting the funding, getting the legislative approval, having those discussions with leadership about deciding to add the screen.

So when you look at the time frames that have elapsed -- for SCID and CCHD for example, those are the ones that we really have time frames on -- we don't have that, we don't have the date for when they said yes, we have approval and funding in place.

Because that's one step that would actually be very helpful, I think, for this committee to say, how long did it take to get approval and funding? Okay, then once you had approval and funding, how long did it take after that to implement?

Because my gut feeling is that the implementation doesn't take very long -- that one to three years is a realistic time frame. It's these four steps before that, that slow us down.

MEMBER BOTKIN: Jeff Botkin. It seems to me that some of this, too, is an artifact

of how the questions are being asked, because I think your surveys about feasibility are really targeted towards isolated conditions -- you know, all other things being equal, how long would it take you to bring this on board?

But I think, it seems to me that what we're seeing is -- given the pace at which this committee is recommending conditions -- that they're in competition with one another. And it may take time to get CCHD on board because folks are working on SCID.

Then it's going to take additional time to get LSDs on board because they're working on CCHD. And I'm not sure our data collection is sort of capturing the fact that these conditions are in competition with one another.

MR. OJODU: Dr. Shone, did you want to add something to that? You were moving and fidgeting. Dr. Shone from New Jersey.

DR. SHONE: I would say, I am not here representing New Jersey.

MR. OJODU: Oh that's right, NewSTEPs.

DR. SHONE: I guess my face gave me away. I agree, 100 percent, with that comment, because the pace at which disorders are being added is impossible for programs to keep up with. Excuse my voice.

And so, and I will say to Dr. Chen's point earlier, the reason the story continues to be implementation is because that's all we're doing is implementing.

We don't have the time to say, hang on a second, let's go back and look at everything that -- or let's go back and look at what we implemented. And that's the reality of the situation.

And so, hopefully now we can take a little bit of a breath, with nothing currently in the pipeline, looking at the pilot study workgroup that I sat on with you, Dr. Botkin, and sort of reassess all this, and see where do we go from here.

But I would say that, my comment -- having participated in multiple public health systems impact and sitting on the group that came up with the questions -- is that, that those first

four or five steps can, perhaps, take one to three years, and then implementation's one to three years.

So you're looking at, like two to six years before something comes out of here that acts -- and reality, and the data that Dr. Sontag and Mr. Ojodu presented bear that true. And so that's, I think, the reality of the situation that we've faced over the last few years.

DR. BERBERICH: Stan Berberich from the State Hygienic Laboratory at the University of Iowa. I'd like to make a comment that I know, from our programs, are impacted, and that is that the public health assessment, which explicitly looks at the feasibility of that, technically, are you able to do it, and the resources needed.

But one of the things that is not explicitly identified as one of the components of a public health assessment is: is it appropriate to impact a population as a mandate for a condition that, in fact, may have enough uncertainty embedded within it that it's -- it would be classified more

as research activities than falling under an actual state mandate, where the state asserts its authority over the rights of the parents to say no, your kid will be screened for this?

And I think that's one of the things that I think if we would include that consideration and component within the public health assessment -- so it's not just the capabilities of the laboratory doing something, but it's actually the appropriateness that the states have to address when they impose something upon their population, and there's a responsibility that goes with that.

DR. TARINI: Beth Tarini, AAP. It occurred to me -- given my time on the state committee -- that there have been discussions in the last year about the FDA, the requirement, I believe, for an FDA approval of the kit, for the test used, before the implementation can go forward in the lab.

Can you comment on what are the -- what is the state of that? Is that a true role within -- so, what is the role of that, and what are the barriers to that in this process, if any?

MR. OJODU: An FDA-approved kit enhances, but it's not necessary for the screening of conditions.

MEMBER MATERN: Dieter Matern. I think, however, that some states have statutes that indicate they have to use an FDA-approved kit for screening.

MR. OJODU: I am unaware of a state that actually has a statute that says that specifically. I do not know of any state that actually says, there needs to be an FDA approved kit for screening, or else they would not be able to bring SCID on, until, you know, there was a commercially available kit in December of last year.

So, yes. I -- it certainly helps in, you know, some states in --

(Off microphone question)

MR. OJODU: No.

(Off microphone question)

MR. OJODU: Not at the moment.

DR. GREENE: Two things, one is, Dr. Tarini, that -- Carol Greene, SIMD. Dr. Tarini's

question sparked another round of very interesting discussion about the reasons for the length of time it takes.

I did not hear anybody respond to what I thought was the core part of the question, which is: given that we've seen some maps that show that at the time a decision was made to add something to the RUSP, that two or three states were screening, and then it takes another more than five years to bring everybody on board.

How does that relate to the comments that were made in discussion of going forward, that well, we must be ready because two states are screening?

So I just wanted to restate that as -- maybe just as a comment, since there doesn't seem to be much of an answer beyond the truth, that it's complicated.

And I think someone just recently brought up a really interesting question about whether in the feasibility or the readiness for implementation, states should be asked about the

question of: is this ready for a population screening, or is it research?

And that is a really interesting question that could lead to a lot of discussion about the dynamic between the states and the federal government.

But one of the interesting questions is, I think the states are being asked a hypothetical question, should this committee, the members of the committee there, decide, and the Secretary agree that it's ready for population screening, when would the states be implementing -- when would the states be able to implement?

So I'm not terribly sure that the states need to be asked -- in the state's opinion -- is it ready for population screening or research, because that puts the burden on each state to make that decision, where there is this committee that, whose responsibility it is to make that decision.

CHAIRPERSON BOCCHINI: Cathy?

MEMBER WICKLUND: So, in just listening to all this discussion, is there a way or

a place that we can really have some further discussions about how we're going to collect the data to see if the decisions we made are actually improving health outcomes?

What would be the process of taking the condition off the RUSP if we have, to my knowledge, right, no process for that at this point in time?

And, I don't know, I just think -- you know, our decisions are going to get more difficult and difficult as we go on down this road, you know, more rare disorders with less evidence.

And that decision matrix, I mean, I don't know if it's a time to look at that again and -- I'm just having a hard time with, you know, using the matrix in a way that I think we intended for it to be used, and the difficulty with the conditions that are being brought up now, and being true to the level of evidence that we think it has, as we make these decisions.

So, and I just, I don't know if, like, we don't have anything in the pipeline, and is it time now to have more dedicated discussions? With

so much coming up right now, we kind of talk about it, but I don't feel like we're actually making progress in coming to an actual decision on how to deal with this.

CHAIRPERSON BOCCHINI: Yes, and I think that's clearly a good point. And I think that part of the goal of the different workgroups is to kind of reframe the information that's needed and what might be needed before a condition goes through to Nomination and Prioritization Workgroup.

And I think -- so that's number one. And number two, I think, from this discussion, it's very clear that outcome data is really important, and we would -- we need to get there.

And I think that's one of the things that as a committee, that we might start looking at, and trying to develop the consortium that Coleen brought up, about how can we put together what's needed to get this kind of data to kind of give feedback to the Committee about outcomes for each of the conditions that have been placed on the RUSP.

And I think that's a really important

goal. And so those would be, I think, from this kind of discussion, those are the kinds of things that come out, that would then end up becoming items for the Committee to kind of look forward, then.

DR. SONTAG: So I would just like to throw in that I see some people in the audience who are very involved in the NBSTRN work and some of the other databases that are out there for long-term follow-up pieces. So this is work that's funded by NIH to collect that, those outcome data.

CHAIRPERSON BOCCHINI: Yes.

DR. SONTAG: So, I think we have systems in place. We now need to utilize them and get that information back.

CHAIRPERSON BOCCHINI: Right. And this discussion was really about implementation, and so I think that's clearly what the focus of this presentation was.

But I think you're right, that we've got to kind of look at all of the rest of the things that are already in place now, kind of put them together in a way that we have the data that we need. Joan?

MEMBER SCOTT: Yes. I would just make the comment that I think we do need to separate -- maybe I'm echoing what you just said, but need to just separate out two separate problems.

The decision matrix is a tool to, you know, look at the data, and the quantity and the quality of the data, to help us make decisions, and that's one issue.

The ability to collect long-term outcomes is another problem, and I don't think the inability to collect long-term outcomes data necessarily should be the basis for changing, you know, our decision. So, I mean, they're separate problems --

MEMBER WICKLUND: Yes.

MEMBER SCOTT: -- with separate solutions.

MEMBER WICKLUND: I completely agree. I wasn't implying they were tied together. If I did, I didn't mean to.

CHAIRPERSON BOCCHINI: I -- yes, I think, two separate things you brought up, no

question. Yes. I've got Coleen first, and then --

MEMBER BOYLE: I was just going to add a third component to that, which was, to me, you know, one is the decision matrix, and a review of how well it's working or not.

The second would -- I mean, these may be future business items, which is later in the day, the second one would be to actually have a -- more of a real time -- and I know you guys are working and you have the infrastructure there in place, but a real time sense of other than what we're at at this very gross state level now, to actually understand better how implementation is occurring, you know, at the more refined level.

And then the third, which would be the, obviously, the most important in some ways, is really trying to understand the impact of the program. You know, is it really having the anticipated health benefit from early pre-symptom identification?

DR. GREENE: And directly related to that is that the Committee will remember that the

Committee endorsed the work of the subcommittee on long-term follow-up.

And the paper that is specifically outlining a framework to do the -- a framework of what data needs to be collected to answer the question, are babies benefitting, has been submitted.

And we will hopefully see the work of this committee published, that will help the Committee to decide how to go forward with exactly that process.

CHAIRPERSON BOCCHINI: Okay, microphone.

DR. COMEAU: Thank you. Anne Comeau from Massachusetts. I really don't want to lose what Dr. Berberich brought up. And Dr. Greene, I disagree with you strongly, because it's under state authority that we do newborn screening. It's under state authority that we take parents' rights away from them.

So, if we don't know enough about a condition to mandate that all parents give up their

rights so that we can collect data in order to determine whether or not a condition should be screened, we're doing research.

We are doing research. And I think something has been lost in this committee. And perhaps it's because of the matrix, but some place we've lost this very important responsibility to all of us, to the entire population, that we're doing research when we don't know that these disorders are worthy of mandating screening.

I think one telling piece of information might be that if we look at all of the states who are screening for the LSDs, whatever, they're doing so by legislative mandate. They haven't gone through their state committee's process to say, this is a good thing for us to do.

They might look to the RUSP, but if it's a really good thing to do and a really good thing to take parents' rights away, the states are going to do it whether the RUSP -- they're going to do it ahead of time. They're going to say, hey, come along with us. Here's some data. We've got some

good data for you.

And to say, well something's on the RUSP so it's not a study, that's just semantics. And I think that we owe our population more than that. We're doing studies, and we need to say, we don't know.

People will still want to participate in studies. People will still want to have their data go forward, to give benefit to future generations.

They'll want to do that more so if we're honest with them from the very beginning to say, we don't know. We can't guarantee you that if we screen your baby, there's going to be a good outcome.

When we do have those data, the states will mandate it. Until then, we need to be saying, we're running studies, and we're doing so with your help, looking to the future.

I think we've lost something, and I think it's a shame, because I think, when I joined Evidence Review -- and I think Evidence Review is still doing a phenomenal amount of work to gather

the available data there -- I was so excited.

I thought, we're going forward in a great way now. People are going to consider the data, and decide whether or not these conditions meet criteria for mandate.

I'm not convinced that that's what's happening. And that doesn't mean that I don't want a lot of these conditions screened for, but I'm not sure that the mechanism by which we're pushing the screening on our population is going to benefit newborn screening.

In fact, it makes me worried that when -- if any of these go badly, it's going to put the rest of the program in question. Our populations have to trust us. As public health people, they have to trust us.

And I thank the members of the Committee who enter into the discussions about whether or not this is the right thing to do. And I hope that we can go forward with more of that. Thank you.

DR. BERRY: Sue Berry from the University of Minnesota. I just want to pick up on

the theme that Marci presented and re-emphasize the need for collaborative activity on the part of all the HHS entities, with regard to long-term follow-up.

It's certainly, and I think, in the mission of all of the agencies to participate. Research from NIH, surveillance from CDC and service provision from HRSA have to go hand-in-hand. I know that was part of the Newborn Screening Saves Lives Act.

And we have some tools, like the NBSTRN's LPDR, long term pediatric data resource. I'd really like to see us be able to emphasize the utility of these and build upon them so we actually have uniform data sets. Thank you.

CHAIRPERSON BOCCHINI: Thank you.

DR. CAGGANA: Hi, I'm Michele Caggana from New York. As far as the discussion, it's been interesting to observe, yesterday and today. I just wanted to bring everybody's attention to some other things that are going on in Programs.

So, we have implementation of new

conditions, we have recommendations from the Committee. So we sort of deal with that on one level. And then several meetings ago we had the whole timeliness discussion.

That has really put a lot of onus on Programs to sort of figure out, look at how we can improve our timing, all the while adding new conditions and adding molecular components.

So, don't forget the timeliness issue, because it's actually been a lot of work for Programs, and great strides have been made, but we're all working towards improving that.

And then when we talk about, as Dr. Berry just said, the impact on outcomes. The systems are in place, but honestly, there's nobody home to be able to do the work.

And there has to be a way in which there's some other funding mechanism that will allow a person to be in shop, and have it their sole responsibility to do this work. It's not trivial.

And when you're asking providers for information, they want to help, but there's

multiple registries out there. There's duplicative efforts. There's competing interests. There's public health, there's private, you know, private registries.

There's the ones that we discussed that are federally funded. And every time we sort of bring this to the attention of our clinicians, they want to do it, but they're already doing this, and they're already doing the other.

So we really do need someone in Programs to sort of take this responsibility and manage this on a day to day level. And the problem now in Programs is everybody has multiple jobs. And so it becomes very difficult to do anything in a real concentrated way. Thank you.

MR. OJODU: Just, Michele, thank you, Dr. Caggana. We appreciate that, those comments, in light of the fact that, you know, we talk a lot about the newborn screening data repository, the national repository.

States that are putting information in there are doing it on a voluntary basis. They're

putting information at their own time, because we hope they see value in it. And, you know, most of these are unfunded.

And, you know, it gives a certain appreciation to all of the other layers of variable activities that we've heard here, so thank you for that.

CHAIRPERSON BOCCHINI: In the interest of time we're going to give Tina the last comment, and then we're going to have to move on.

MEMBER URV: Real quick. I just wanted to say, with the long-term follow-up, NIH has the perfect opportunity to step in. Researchers can put in grants to follow these kids that are identified in newborn screening.

I know when we started SCID, the kids were identified. We were begging researchers, please, you know, start following these children now. Put in an R01.

And I'd like to encourage the family groups that are advocating to add these conditions to newborn screening, that continue to work with

their research community to encourage their research community to continue following these kids.

And there are funding mechanisms and a way to do that. So I just -- follow up the kids. We could do that. Yes, it's there.

CHAIRPERSON BOCCHINI: Okay, thank you.

MEMBER BOYLE: Can I just say one more thing? I'll be quick.

CHAIRPERSON BOCCHINI: Okay.

MEMBER BOYLE: Okay.

CHAIRPERSON BOCCHINI: All right. I'll give --

MEMBER BOYLE: So just --

CHAIRPERSON BOCCHINI: -- you the last comment.

MEMBER BOYLE: Okay. This Coleen Boyle. Just to give an analogy around the dedicated funds, so when EDHI rolled out a number of years ago, there was actually dedicated funds set aside for HRSA as well as for CDC.

CDC's was to develop the information system and structure for long-term follow-up. Now it's not been without its challenges, but I also think it's made significant progress, and similarly the dedicated resources for this one condition.

So I do feel like that -- and I hear Michele's concern. I hear -- we hear it over and over again. You know, we experience that same thing in our own world, in terms of trying to support CCHD roll-out.

I mean, I do feel like we, as a committee, we have to somehow grapple with this, this -- there's dollars that need to be going to this area. I mean, you know, as a federal person, I recognize that.

But it is something that we have to show the need for, and how money going to this area will really improve the quality of the services that are provided.

CHAIRPERSON BOCCHINI: Jeffrey?

MEMBER BOTKIN: Yes, just really to reinforce that, so I can be quick. And I think

we've heard a presentation about three recent conditions this morning, and I think NewSTEPs has done, really, an extraordinary job.

But we've got no information on what's happening with these screening programs, in terms of how many kids are being identified. And again, that's not a criticism, but I think it's consistent with what I'm hearing at least, is that there is, that there aren't dedicated staff at states to help manages these data.

And I think was a point I'm going to make, too, probably, with the education activities, is that they don't have a dedicated -- most states don't have dedicated activities staff for that, too.

So maybe states are systematically under-estimating the kit fee increases that ought to be part of these new screening modalities. You know, an extra couple bucks on a kit fee could pay for folks that would be data managers and education coordinators that might substantially improve the system for a fairly modest fee.

I mean, our -- Utah's $105 or something now. For 107 bucks we could have a dedicated person to really deal with a lot of these sorts of issues. So, I think staffing might be something the Committee should pay specific attention to.

CHAIRPERSON BOCCHINI: Matern?

MEMBER MATERN: Sorry. Dieter Matern. Okay. So, I think it's always great to have money to throw at things and do things that way, but I think we also should remember that there is a federally funded system, or initially funded, called R4S, that data shows that if California, for example, used it on a daily basis, they would reduce their false positive rate for the MS/MS, or the amino acid acetyl-L-carnitine test, by 90 percent.

Nobody did the calculation how many FTE and money it would save in follow-up of -- unnecessary follow-up, but I think that it should be considered, and we probably should remind people to use those free tools to save time and money.

MEMBER LOREY: You'll be happy to know they're moving in that direction.

CHAIRPERSON BOCCHINI: All right. Well, I want to thank Marci and Jelili for an excellent presentation. And clearly, they've raised a number of questions, comments, that I think are really important to the Committee, so we'll bring those forward. So thank you.

So, at this point we have two public comments that are scheduled. So if Bill Morris will come forward.

MR. MORRIS: I'm kind of short, but not that short.

Good morning, thank you. My name is Bill Morris and I'm the father of four boys. Two of my sons are affected by two different recessive disorders.

My son Seth has PKU, or phenylketonuria, and was saved by the Texas Newborn Screening Program. He's perfectly healthy. My fourth son, Grayson, died a week before his first birthday from Krabbe's disease in my arms. He was not identified through screening.

I am also a special needs pediatric

nurse with 18 years of experience. I want to again bring up to this committee and caution them about the need for newborn screening education of health care professionals, and parents about the process and intent of newborn screening. It is not consistently happening.

As this body recommends additional conditions to the RUSP, we are -- this problem is being compounded. We have health care professionals still calling newborn screening the PKU test.

We have a dangerous ignorance about proper sample collection, need for timely transport of samples, receiving, verifying results, reporting out of results and the ability of parents to gain information about and referral to specialty care and treatment.

All of these factors can stack into a perfect storm, causing delays in diagnosis and treatment. They can make a difference in an infant being saved by newborn screening like my son Seth, or being irreparably harmed.

We have an urgent need for a uniform set of educational guidelines for health care providers during their training, and for parents during the prenatal period.

You, the Committee, are in a perfect position to advise the Secretary to develop this set of guidelines, and help us establish newborn screening so that everyone knows that it exists.

I thank you for your continued work and dedication, and as a parent, I thank you for the care that you all take, and the fact that you allow us parents to approach you and give you our point of view and show you the emotions that have affected our lives in newborn screening. Thank you.

CHAIRPERSON BOCCHINI: Thank you, Mr. Morris, for your comments. We appreciate them. Next, we have Mr. Dean Suhr of the MLD Foundation.

MR. SUHR: Good morning Mr. Chairman and the Committee. I'm here as Dean Suhr with the MLD Foundation, but I kind of want to take that hat off.

We organized a meeting the day before

this committee met, so this was Wednesday, and about 26 of us gathered under the auspices of a RUSP round table.

And it literally was that. It was an opportunity for people from a variety of perspectives to get together. The goal, the stated goal was to share perspectives, to learn from each other, to put issues on the table, to talk about challenges, opportunities, not so much about solutions, but just to understand what the perspectives of others were.

Our focus was to be the viable therapy, and that requirement for the RUSP, however, we wandered into a lot of topics, and I just wanted to briefly share with the committee members that weren't there, a little bit about that.

Who was there? Public Health and Labs Committee members, some clinicians, pediatricians, neurologists, a genetic counselor, industry from the pharma side, industry from the genomic sequencing side, certainly a couple of advocacy groups.

And we had somebody who had a sociology hat on as well, and I'm probably mislabeling that title, but that was the perspective that he brought to the table. So it was a broad mix of people, and as I said, we just had an open conversation.

We started off with a little bit of history about this committee and where it came from, so that we were all well-grounded in the roots of the Committee and of the RUSP and its requirements. We talked a little bit about its evolution.

And then we got going on a whole list of topics, and I'm not going to -- I'm just going to blurt them out, kind of in bullet form, in respect for the time here, and because the thoughts are not completely organized from all of the notes, in terms of conclusions.

We will summarize this at newbornscreening.us, which is the website we've been organizing this under, and we'll share this back with the Committee in a more formal way if that's of interest to you.

But we talked a lot about quality of life

as a metric. This is evidence-based screening. We acknowledge that and we support that. But quality of life is much more difficult to score. So, particularly, the sociologist input into that was very insightful. We talked about the challenges of that.

The impact of newborn screening on families, carriers, care givers, societies, as those extended beneficiaries, and we heard that discussion yesterday in the ALD discussion as to what's part of your criteria, what's not.

Clearly, newborn screening is a public health thing, and it affects the public, and that circle can get very, very small, and very, very large.

Interesting comment about this committee, this is not the Newborn Screening Committee. Talk a lot about newborn screening, but this is, this has got a -- this committee has a broader charter in terms of heritable diseases in newborns and children. And so there's some opportunity, and perhaps some additional burden

that may come with that.

Newborn screening is clearly part of public health, as a comment just a few minutes ago, where does research fit in to newborn screening as a public health initiative, and what does it mean as we tag along research? We discussed that a bit. We learned about Early Check and that program as well.

A little bit on viable therapy. We discussed that there is always a treatment. And knowledge is power. If you know that you have a disease or a condition, no matter when that onset is, and of course, there's a lot of ethical issues that we talked about as well, as to who wants or needs to know what and when. But if you know what's going on, you're more likely to make a decision to get an appropriate treatment. So we talked about that.

Funding, funding and approval, we just talked about that here. That is a clear role that advocacy can take on. It's not something that can be driven as directly from the Committee, but with

knowledge, for us, we can start pounding on different doors with different messages, to help with funding.

And then there was a discussion that was inspired by some of the industry people who are moving on in different directions with regard to how they're developing therapies and some of the screens, particularly genomic screening.

And this idea that the public health system is perhaps missing an opportunity, might be overtaken by an opportunity, or needs to embrace an opportunity for what's happening in the private side, the commercial side of the world, with regard to crowd sourcing, capitalistic enterprises, genomic screening, the access that the public -- some of the public, not all of the public, and I know the charter here is much broader, so there's plusses and minuses, but access to different methodologies of testing at different price levels, and different choices for that.

But we need to acknowledge that that's happening and consider that.

So the next steps -- as I say, we put a lot on the table, and I think the next step is going to be to schedule that round table again, probably in six months or whatever it is to the February meeting, which is the in-person meeting, and follow that same agenda, and get a little more focus in some specific issues where we can drive to maybe some actionable conclusions.

But we achieved our goals, which was to share perspectives. And the feedback, universally, from all, from industry, from committee members, from public health, actually everybody that spoke to me individually said that just being able to talk about these issues in a somewhat informal manner was productive.

So I thank you all for time for that. I do thank you also for the hard work that you do. This is not easy work. Just the evidence review is not easy, but it is so important to families, and we do thank you for it.

CHAIRPERSON BOCCHINI: Thank you, Mr. Suhr. So since we're running a little bit late,

what I thought we would do is take our ten minute break now, and then get into the reports of the three workgroups. But it has to be a quick ten minutes.

So we'll start promptly at 5 after 11:00, and I would like, before any committee member leaves, I would like the Committee to come forward, so we're going to take a photo of the entire committee. Then you're free to move on. All right.

(Off microphone discussion)

CHAIRPERSON BOCCHINI: Oh okay. All right. Our photographer has not yet arrived, so go do what you need to do and them come back. All right.

(Whereupon, the foregoing matter went off the record at 10:53 a.m. and went back on the record at 11:09 a.m.)

CHAIRPERSON BOCCHINI: All right, we're going to get started. All right, at this time we're going to have reports from each of the three workgroups. And the first workgroup update comes from the Cost Analysis Workgroup, and Dr. Lisa

Prosser mostly will provide this update for us.

DR. PROSSER: All right, thank you. Good morning. So, this is a report back from the Cost Analysis Workgroup. We met yesterday for the first time, formally, but we've met a few times earlier by telephone, having some framing conversations around the charge and next steps for this group.

So this slide shows the members of the workgroup, representing all the key stakeholder groups. I know many of the folks are in the room here. I believe Scott Grosse is on the line as well, so please jump in and add to any of the summary as I go through.

Okay, so since this is the first time we have reported back to the Committee, we thought we'd start with the charge of the workgroup, and that is to consider methods to assess the cost of newborn screening expansion as required by the newly re-authorized legislation.

So the deliverable of this workgroup is to report with recommendations to the acting -- on

how to incorporate a cost assessment into the evidence review.

And just to frame this a little bit more broadly, in terms of the evidence review, it's not that we currently ignore costs or don't include economic evaluation entirely, it's part of our charge, as part of the evidence review, to include any type of economic evaluation information.

We include that in the literature search, and we review it if it's available. But what typically happens is that for most of the conditions that we've reviewed so far, there's very little or no data that's available.

So when the conditions are being considered by the Committee, clearly cost is one aspect, or cost effectiveness or cost benefit, and we'll talk about where we're likely to go there, and typically there is very little purview.

So in the context of that, we're trying to figure out how we can incorporate the cost assessment so the collection of some level of data, similar to the way that we integrated decision

modeling to be able to provide population health benefits based on what's available in the evidence review, but to be able to work with the states, with APHL and NewSTEPs, to figure out how we could collect some of the data, at least on the cost of screening, incremental cost of screening, to be able to inform committee decisions.

So the questions we addressed are what costs of the newborn screening expansion should be included within a condition review, to better inform the Committee, what are the critical data elements needed to address the costs of newborn screening expansion, and in a couple of slides we'll go through what the key cost categories are. What's the availability and feasibility of collecting this data, especially within the newly mandated nine-month time frame for the evidence review?

What will the data sources be and who will provide these data? Will this be contingent, required for the nominator to do? That's probably not feasible but to be discussed. And how could

this impact the nomination and review process?

And so the question here is, you know, we could frame the question, but we'll come back to the Committee with the question as to how do you see this being included in the condition at the Committee's deliberations?

And this is a case where -- something where, similar to the public health impact, that this would be added to the matrix as a new criterion, or is this something that will be incorporated into the Public Health Assessment, or considered separately as an additional piece of evidence?

I think those questions should be addressed within this workgroup and with the Committee.

So just a little bit of background, so in terms of, you know, there are many types of economic evaluation, starting with the most comprehensive, which would be a full blown cost effectiveness analysis or a cost benefit analysis of comparing newborn screening to clinical identification on when a condition is being

considered.

But we've had discussions within the group -- workgroup and here, that, you know, creating and developing a new cost effectiveness or cost benefit analysis is really not feasible within the nine-month time frame.

And so what we're looking at are considering a budget impact analysis, which evaluates the net change in financial expenditures for a health care system over a given time frame.

So this is the budget holder perspective. So we'll be measuring costs and not looking at cost benefit or cost effectiveness, and not cost per unit of health on gain.

So this slide shows some of the major cost categories when we're considering the incremental costs that are considered for adding a new condition.

So there are costs to public health departments, in terms of laboratory testing, as well as short term follow-up and tracking, and we do consider those to be part of the screening costs.

There are downstream costs to the health care systems as well as to families in terms of clinical follow-ups from screening all the way through diagnosis.

So there are direct costs to the health care system. There are out-of-pocket costs from families. There are time costs from families included with all the medical care associated, long term management, both for target conditions as well as secondary conditions.

So if we're thinking about the example of X-ALD, that there is a category of newborns that will be identified with the mutation but do not have any symptoms. You know, they will now need to be followed throughout their lifetime, and some of them may not demonstrate any symptoms until very late in their lifetime, if at all.

And so there will be follow-up costs associated with management of those patients as well, over the lifetime. That's something that could be considered. I think that will likely be outside of the scope of what we will try to quantify.

But it's something that we could include as, you know, this is a cost that is out there but we are not able to quantify within this specific effort.

And just to highlight that, again, the cost of newborn screening expansion is really much more than the laboratory costs or the costs of the initial screening.

To add to the complexity, you know, there is substantial variability across states, in terms of the costs when a condition is added to the panel.

So not just are there differences in -- so there are fixed costs, but there are variable costs. So the variable costs will change, depending with the volume that's going through that laboratory. That could vary state by state.

But there are, as we heard earlier today and yesterday -- that some states were, you know -- one versus two screenings, and right there is the difference in current costs that is really not, you know, from our perspective, it's not a measurement

issue.

It's not that we can't measure that, but that there is this variability, that if we're trying to report what is the actual cost of screening, that there is a difference between states that fall into those two categories, that needs to be captured within a cost analysis.

And then again, there is additional complexity in that some states are not screening for this condition but are contracting to other laboratories and specialty centers that may have different cost structures.

So when we're thinking about creating a framework for a cost analysis, we want to be sure that we include all these different types of arrangements that could occur.

So some of the challenges specific to the workgroup is to think about how we can create a framework for a cost analysis that will provide useful information to the Committee while still trying to consider some of these downstream costs that are really important when we're thinking about

the cost effectiveness of newborn screening or the cost benefit.

Again, variability in states, feasibility that we're trying to incorporate this into the nine-month evidence review framework, that we'll have to think about, what's the scope of the analysis, both in terms of what costs are included, how long we're going to consider follow-up.

We'll be looking at a one-year time frame following screening, two years, five years, similar to how we have put parameters around what's included within the decision modeling, population level estimates that we're focusing on key health outcomes within a certain period of time.

We'll have to think about how we can include that in the framework here. We'll be conducting the cost analysis, and how this information will be considered by the Committee. And this is really critical in terms of, you know, how we frame this cost analysis to make sure that it's of use to the Committee.

So, you know, our initial conversations

is that a budget impact cost analysis approach will be the most feasible. That will be focusing on the common cost categories associated with newborn screening expansion.

We'll be working through how to make these assumptions clear, how to identify a variability of ranges, and in particular it's really not just that there are ranges, but they're getting different scenarios, the states that fit into different types of screening algorithms, and determine the scope.

So what are the cost categories, the time horizon, and what's the perspective? So really, at the state level, so the cost -- so cost information right now is being used, at the state level, incorporate into state level decisions into how they implement screening, will be very important at the state level.

And the question is, you know, how can we provide information that's useful both to the Committee, but will also be useful to states as they're making these decisions?

So the next steps are to review the methods that have been used in -- for incorporating cost estimates for MPS I that were included in the public health assessment, to develop a draft template for estimating these incremental costs, coordinating efforts with other groups here and elsewhere to make sure that we can have leverage everything that's happening.

And what we'd also like to propose doing is to prepare a range of cost estimates retrospectively for X-ALD to get a sense for how long and how feasible it is in terms of what we can include in that scope.

And then finally, at the -- we would really like to -- there was a lot of discussion yesterday about how we could leverage this to be useful at the state level as well, so thinking if there's a way that we could develop a framework that provided estimates that were useful for the committee evaluation, but that could also be translated into a tool that could be used by states to help them estimate what the cost would be for

their individual states as they consider implementation.

So, I'm just going to pause there. And I don't know if Scott Grosse is on the phone, if he wants to chime in, if any others on the Committee have additional comments.

CHAIRPERSON BOCCHINI: Dieter?

MEMBER MATERN: Dieter Matern. As far as I know, in Washington State, they are supposed to do a cost analysis before they implement any new condition.

DR. PROSSER: Yes.

MEMBER MATERN: Is there any --

DR. PROSSER: That's true. And we have several members on the Committee that have been involved in that effort, and so we'll be working closely with them to see what pieces of that would be feasible to implement here. Yes.

MEMBER WILLIAMS: So, this is very interesting. Way back when I first started coming to the Committee meetings, even before I was a member, it was said that the decisions to add in

conditions would not include costs.

So adding this to the matrix needs to be separate conversation, and to state, in that, because I don't see that there is a need to put that part in the matrix. And you mentioned it here as a part of it.

So if we're going to talk about costs and all of that, I just want to be very clear that we should keep it as a separate conversation.

MS. PROSSER: Right. Thank you.

CHAIRPERSON BOCCHINI: Other comments? All right.

MS. PROSSER: Okay, great. Thanks. We'll look forward to input as we start working further.

MR. BANBURY: Thank you, Lisa. Appreciate it. Next on the agenda is Dr. Botkin, who will present a report on the activities of the Pilot Study Workgroup.

MEMBER BOTKIN: All right, thank you. Good morning. I'm going to try to move through a relatively few slides fairly quickly to get some

feedback from the group.

Pilot Studies group has been in existence for about a year or so. This is -- yesterday was our first opportunity to get together as a physical group, so it was a nice opportunity to get a number of ideas out on the table for consideration.

So, our plan is to try to develop, before the next in-person meeting, a formal set of recommendations that will come to the Committee for consideration. So here's our membership. I hope I haven't missed anybody, terrific group.

So the rationale for the workgroup, of course, is this general recognition, the evidence review process requires actual evidence. But there's a lot of challenges that we're very familiar with, certainly over the last day or so, have been highlighted in particular.

These are rare conditions, for the most part. Population-based research is complex and expensive. And I'll comment a little bit about Section 12, but the Newborn Screening Saves Lives

Reauthorization Act that requires informed consent for the use of dried blood spots for federally funded research.

So the consent issues here are a significant challenge for us. And as folks know, this -- the Section 12 that came through last December requires parental consent for use of dried blood spots, and really eliminates the ability to conduct federally funded research that involves adding a new screening test on a pilot basis, on an opt-out basis, or with a simplified consent process.

Now, our research and other groups' research have pretty clearly shown that the general population of parents want to know about these activities and they want to have a choice.

So the Reauthorization Act was speaking really directly to a public want and need in this respect, but I think it reflects unanticipated consequences as the legislation met a legitimate public demand but now has some serious consequences for how we conduct our work, and I think sets up an

unfortunate ethical dilemma between the need to develop evidence for the welfare of children and the need to respond to peoples' interest in being adequately informed and having a choice about these sorts of activities.

The primary challenge here is that to date, we have not figured out how to do consent in a way that doesn't substantially reduce uptake, making pilot studies, if you will, that much more complicated, expensive and difficult to conduct. So again, a legitimate ethical dilemma here on how best to do this type of work.

So, as folks are aware, there is Notice of Proposed Rulemaking forthcoming. OHRP actually will be making some guidance statements about the Reauthorization Act in Section 12 in the near future. But there's also a Notice of Proposed Rulemaking that may well change human subjects regulations.

And just to remind folks, at least my impression of the process is -- is that will require an additional comment period, and then final rules

will be implemented later.

So we may well be several years down the road for any actual changes in the regulations. So folks should not look to this as any sort of short term potential fix to the challenge that we're facing now in this domain.

So, for the time being, so-called pilot studies in this context may require either consent or to be conducted through state-mandated systems. And Anne Comeau's comments certainly are directly on target here.

This is not the best way to conduct evidence gathering, is through mandated systems, for exactly the reasons that she had articulated. If we don't really know that these are beneficial for kids, they shouldn't be part of mandated systems.

On the other hand, is this a ethically tolerable end-around to what's otherwise another intolerable system, which is not having data to be able to make informed decisions for the welfare of kids and families?

So here's our charge to the Committee. Recognize and support current efforts regarding pilot studies and evaluation, secondly, identify other resources that could support pilot studies and evaluation.

And then thirdly, topic of today's conversation, identify the information required by the Committee to move a nominated condition into the evidence review process, i.e. define the minimum pilot study data required for a condition to be accepted for evidence review, so.

Emphasizing the question is what data are the minimum necessary to move a nominated condition to the evidence review process, understanding that under the new legislation, we have an accelerated process where the Committee needs to make relatively -- have a quick and efficient process to come to its conclusions.

So what we're not talking about here, and I think, keep this in mind as we think about these criteria, we're not talking about what evidence is necessary to actually approve a

condition for the RUSP, but rather to move it from the nominated state to the evidence review state.

So here's what our form says now. For a nominated condition to be considered, there are three core requirements, validation of laboratory test, widely available confirmatory testing with a sensitive and specific diagnostic test, and three, a prospective population-based pilot study.

Now each of these deserves attention, of course. The primary focus for today's conversation, again, is going to be this third one. What do we mean by a prospective population-based pilot study?

So in the absence of a pilot study, I think the history of this committee clearly shows that that's been consistently identified as a fault that will stop the process for a variety of different conditions.

So in many circumstances for many conditions over the past, the Committee has said, you don't have a pilot study that really adequately evaluates this screening for this condition, so the

process will not move forward.

So clearly, additional clarity on the nature of what sort of pilot study would be necessary for the purposes of this committee is necessary.

So pilot studies is a term used in the literature for a variety of types of studies in this domain, test validation studies, testing of anonymous dried blood spots, sometimes referred to as pilots.

So I think, clearly, the term pilot study is non-specific, and so we don't -- I think we decided that we don't want to try to redefine the words for this context, because it's just too prominently and broadly used, but rather more clarity on the type of study necessary to move a nomination forward.

We've got to get rid of the -- any boundaries around definitional challenges of the notion of a pilot study.

So, this is moving towards very tentative requirements here, and hopefully if I

finish quickly it'll give the committee members a chance to give their own opinion about what we talked about.

So how does the screening test perform in a population-based sample in terms of clinical validity? I think that's the key set of information we're looking for here. It's clinical validity.

Now the existing requirements, as articulated before, are prospective population-based pilot study, perhaps should be rephrased to say, a prospective population-based evaluation of a newborn screening and patient identification.

And I say why I think maybe those words might be helpful. We've gotten away from the notion of a study, because we may well use the experience of mandated state programs, as we did with ALD.

But what seems to be necessary is actual newborn screening of actual babies, and patient identification, in other words, we want

identifiable babies in order to make informed decisions as a committee.

So here are the stipulations that we've discussed. Newborns screened should be identifiable, and their clinical status evaluated to determine the clinical validity of the screening test result.

Okay, so work just with dried blood spots alone, for example, works for validating a test would not be sufficient, is the implication here.

Secondly, at least one affected newborn should be detected through population screening. Sort of goes back to our SCID experience. You know we waited, got the A, if we found a baby, we can now approve this.

Now, nobody would think that one baby is an ideal data set to make these sorts of decisions, but at least trying to set a minimum, you better have found one baby. And that, at least, gives you a little bit of a numerator to determine positive predictive value.

Otherwise you'll have a denominator, but you don't know what the numerator is. You don't know what your positive predictive value is until you actually identify an affected baby.

The evaluation need not demonstrate clinical utility, as long as other data are submitted to address the utility of screening.

Again, I think that's what happened, what we saw with the ALD discussion yesterday, where the New York mandated screening process helped very much with issues around what's the positive predictive value, what's the specificity of the test modality.

It didn't really help us in terms of showing whether screening was beneficial for those babies or not. We've relied on a separate data set that looked at the issues of kids detected through family history versus kids detected through symptomatic presentation.

So, the point here is that it would be ideal if we had the large population-based studies where you could conduct sufficient evaluation to

determine that you had clinical utility, but I think the point here is we're suggesting that we don't make that a requirement to move it to an evidence review process.

And then lastly, the screening evaluation should be conducted in an appropriate population, that is, one that adequately represents the U.S. population that would be screened in newborn screening programs for the condition at hand.

Now we didn't really have enough time to discuss this in particular detail, but part of this goes to the fact that, is data out of Taiwan okay for certain conditions?

And I think the answer would be -- this suggests the answer would be yes if we have reason to believe that the Taiwan population is sufficiently similar to U.S. population to give you adequate data.

If, for a particular condition, the populations have very different structures with respect to certain conditions, then doing screening

in another country may not be sufficient information for a decision making process. At least that's the implication here.

What we have not talked about yet is, once we come to a certain set of determinations or recommendations of these sorts, what sort of process are we going to identify for the Committee to actually come to the conclusions about whether the minimal criteria have been met to move it from the nominated stage into the evidence review stage?

And I think what we want to try to avoid is evidence reviews in order to justify evidence reviews.

On the other hand, we want somebody to be looking at -- with sufficient knowledge and sophistication -- to be able to look at the proposed condition in a way that would make a decision about, okay, this is ready for prime time because it's met the criteria that we've articulated.

All right. I'm going to stop there. Time for other committee members to comment, perhaps, and questions.

CHAIRPERSON BOCCHINI: That was a great summary. Don?

MEMBER BAILEY: Thank you, Jeff. That's a -- you absolutely did an amazing job of summarizing a complex discussion from yesterday. I think it will be -- and I think you made some great points here and we got some good issues and topics to move forward on.

I think we need to go -- and in light, in line with some of the comments that Dr. Wicklund made and also Dr. Comeau, we can step back, because we now do have some time to kind of think about where we are in this whole process, and think about the different components of the decision-making model and how pilot studies fit into the broader picture.

And the way I think about it, at least this morning, is, we've got research, we've got feasibility, we've got pilot testing and we've got program evaluation, and those each play different roles and answer different questions at different times.

And so evidence review starts with the

understanding of the research. And those are carefully defined studies that control variables and try to provide pretty clear answers to the questions, in sometimes artificial settings, but very controlled circumstances, so at least we know what the truth is about certain things.

Feasibility studies are more perceptual, at least in the way I'm thinking here, is that more perceptual studies of the people who would be implementing this program feel like it could work.

Pilot studies would be then, once you think people can do it, and you start -- it -- could it be ramped up into a larger -- in a larger context.

And the program evaluation, and I just agree a certain extent with Dr. Comeau that, because I think program evaluation could be divided into formative and summative evaluation.

And so, formative evaluation is a lot of what Jelili and the APHL group were presenting this morning which is, you know, once we roll this out, how is it working in an implementation way?

And then the summative evaluation is, at the end of the day, was this a good decision? Do we know now that once we ramp this up at a big program level, was it a good thing? Is it resulting in good outcomes?

And some of that is not research, and some of it might be research. If you're re-contacting families, for example, to talk to them about their perceptions of the experience, then that is research and you would have to get consent.

So I think what this committee has done has been great. But I do think we have a good -- it's a good time to step back and say, how do pilot studies fit into the broader sequence of decisions that we need to be made and when, and how do they fit.

MEMBER SCOTT: That actually, your comment sort of raised a question in my mind. Oh, sorry. Joan Scott. You have to hit me on the head with it.

CHAIRPERSON BOCCHINI: It's like they

hit you with it.

MEMBER SCOTT: Well now I've totally forgotten what I was going to ask.

CHAIRPERSON BOCCHINI: You're brain injured.

MEMBER SCOTT: You broke out feasibility studies from pilot studies, and I'm curious about that breakout because part of the -- or should they be separated out, and the ability to do this test on a high throughput public health environment, is that the same or different than the pilot studies that are -- I guess I'm a little confused as to what is the specific information that we're trying to get in the pilot study.

MEMBER BAILEY: Right. I think that's the whole point of what Jeff's presentation is. We need to be asking that question. The feasibility is really, maybe smaller scale efforts to say whether we could take this to scale at some level.

And part that is perceptual and maybe part of it is some, you know, trying it out in two

counties or, you know, in a way, small enough sample. But the pilot study itself, I think, needs to be with a larger ramp up. But feasibility and pilot might -- there's some blurred lines there.

MEMBER BOTKIN: Yes, and it seems to me feasibility would be for various aspects. You might well want a population study that answers the question, can you ramp this test up to a high throughput platform that'll take care of the number of babies in the state?

And then once the test is great, once you know the test is effective, there's a second set of feasibility which is, could your state do it? Because you've got other implementation barriers that maybe present, aside from the test or the efficacy issues.

MEMBER SCOTT: And my second comment was that, I was going back to your very careful removal of the word study, and that you're being agnostic about whether or not a pilot occurs -- can occur in a clinical setting.

And like -- because there's a

legislative mandate to do the testing, and so we have New York data, as an example, as opposed to whether or not it's being done as a research project in the state, where there is informed consent as part of it. Both of those would result in pilot data.

MEMBER BOTKIN: Yes.

DR. TARINI: Beth Tarini, AAP. To add to this discussion of feasibility in pilot studies and definitions and such, we have sister agencies in the room, HRQ, NIH, who, my understanding and experience has been -- have very, I wouldn't call them strict, but certainly defined ideas of what constitutes a pilot study.

I would not submit -- if I were to submit a grant, for instance, to one of these agencies, I would have to, in my pilot study, reach a certain number of metrics, i.e., A, it's feasible, A, I'm able to do it, engage. I can move someone all the way through.

So I think we can certainly lean on the federal partners with their experience about how

they would define pilot studies, pilot projects, whatever you want to call it, so that we don't have to reinvent much of the wheel.

CHAIRPERSON BOCCHINI: I think that I certainly very much like that comment. I would perhaps emphasize that, to some extent, we again, want to be careful about what constitutes adequate pilot study to approve a condition, in which case you'd want to carefully look at all of the parameters to decide what the quality of data is.

And what different decision might be made earlier to say, studies or evaluations of certain types have been done, therefore we're going to move it to the more formal stage.

DR. GREENE: I think possibly Dr. Botkin just said this, but maybe I'm looking at it slightly differently. In preface, Dr. Botkin, you said, let's not use the word study. Let's talk about what questions need to be answered.

And then you specifically used some words like pilot and feasibility, and now we're getting into discussions of the definition of what

is a pilot study and what is a feasibility study.

And I think if you just stick to the -- what questions need to be answered, then you don't have to worry about who defines what as what, and what overlaps.

MEMBER BOTKIN: Yes.

MEMBER PARISI: Yes. Just to add to that -- Melissa Parisi, NIH. In our discussion yesterday, I think we did deliberately think that the use of the word pilot study was to be avoided in this context because we really wanted to say, what are the criteria, the parameters that need to be considered, to move to Evidence Review Workgroup.

And we didn't want to be bound by the preconceived notions of what a pilot study might be for our various agencies or our various groups. So it's a sort of different way of framing the question, but I think it's important to think about in those terms.

DR. BAKER: I just -- oh, Mei Baker from Wisconsin. I just want to add on a little bit. I

really like the word evaluation, because sometimes when you say study, project, that they're automatically equal to research, which is, I think Dr. Greene said it well, is that you, is really intention, what's the whole process of what you want to do?

And I agree with what Dr. Bailey was saying that, it's from my personal experience of through the Pompe, the process, I don't use color anymore, I don't need it. We went through the IRB. We need to think about IRB process, too.

When you receive the funding, you -- through the IRB. So the IRB working with us very closely. We do twice -- do the process, the conclusion is, what's your intention?

And I, honestly the intention is, I want to see how this process in our screening, just acting like we are screening for real, what the process establish -- tells me is really, you know, learned.

So their conclusion is, that's the program evaluation. So we are able to do this

process. So I think we need to keep this in mind to do this work.

MEMBER BOTKIN: Good, thank you.

DR. CHEN: Freddie Chen, IAFP. Can we just clarify, Jeff, the -- I'll just call it pilot study for now, because --

MEMBER BOTKIN: Right.

DR. CHEN: -- what you're workgroup's called. But the idea about having one is not that it's -- that, by itself, is sufficient evidence to them, right? I mean, we're --

MEMBER BOTKIN: Yes.

DR. CHEN: I want to make that distinction very clear, because we've been in this situation before, about to approve a condition, like SCID, where we hadn't even identified a single case yet, and we needed to wait for that one case to come up, and then we felt more comfortable with it, or this situation of approving a condition because we had one small study that worked.

So, I mean, there's the workgroup's work on requirements for a pilot study, which are

separate from the requirements for the evidence -- I mean, the -- at least the matrix. Is that right?

MEMBER BOTKIN: Yes, yes. I think that's great. And I think that's going to challenge our process to a certain extent, given the efficiency that we're being required to address at this point. Because we want the Evidence Review Group to have high quality data in order to get through that quickly.

And I think the challenge, of course, we saw with the ALD is the group going out to collect their own data, because it wasn't in the literature. Now that's a serious problem. But more credit to them that they were able to do that.

But I think we want to try to front load some of those decisions to say, is there quality data out there, while still leaving it up to the Evidence Review Committee and finally the Committee to decide whether the evidence is adequate to -- for a positive finding.

DR. CAGGANA: Hi, Michele Caggana from New York. I just had a question. When you had your

three points up there, the one was establishing clinical validity, and then the other one was finding at least one affected newborn.

I'm having trouble rationalizing how those two are going to occur, because it seems to me you're going to need to really identify quite a few more than at least one. So I don't know if there was discussion on some other number, for validity.

MEMBER BOTKIN: Well, no. I think we're quite open to hearing people's opinions about that issue. I think that, again, probably referring to the, both to SCID and the ALD, were circumstances in which the population-based evaluation didn't turn out to be the critical factor in convincing the Committee that there was sufficient clinical utility in screening, in order to justify putting the condition on the RUSP.

So I think for that reason, we wanted to say that this population-based evaluation need not be of sufficient size and rigor to demonstrate utility. Again, particularly because with things like ALD it'll take many years to figure out, with

the later onset of many of the kids, how well screening works through a pilot.

So we were going to allow the Committee to make a determination about utility based on other data sets, and not necessarily what we're requiring here, the population-based evaluation.

DR. CAGGANA: No, I was -- or, maybe I misspoke. I was talking about validity, the first bullet, and then the second bullet, how you establish clinical validity with only finding one affected.

MEMBER BOTKIN: Okay. Good question.

DR. COMEAU: Can I -- following on that, I -- there's the only one affected, but I also think it might be -- Anne Comeau, Massachusetts. I think it might also be driven by the analyte.

I mean, I think that there is some -- I'm not sure that you need one affected newborn to demonstrate clinical validity. I think you need clinical validity in having a specimen from an affected newborn go through a high throughput screen to say that you can find that affected

newborn.

But I don't think that you have to find that newborn from the population, I mean, because it's a laboratory demonstration of validity of finding the analyte. I --

MEMBER BOTKIN: Okay. Well I'd certainly, personally value additional thought about this. And I think, at least my notion is that by doing the population screen evaluation, and let's imagine you find 20 kids who need clinical evaluation, and none of those kids turns out to have the condition you're looking for.

So, you've learned something. And you don't know whether it's going to turn out to be 50 or 100 until you actually find an affected kid. And then you sort of know, all right, what's the positive predictive value.

Got a wide margin, no doubt, of confidence interval around that, but you've got, it seems to me, more information than you would if you didn't wait until you had that one affected kid. Now you're saying there are alternative methods to

sort of figure it out.

DR. TANKSLEY: And Dieter may address it the same way. I mean, essentially, what -- to prove the clinical validity of the test means essentially validate the test, you have positives, negatives. You have -- you may have a patient specimen, and you could, you can validate the test that way.

I understand, the ability to detect an unknown in a population, I think, is what you're addressing.

MEMBER BOTKIN: So does that support the notion of waiting to have an affected kid, or not?

DR. TANKSLEY: I don't think so.

MEMBER MATERN: I don't think --

DR. TANKSLEY: I don't think so.

MEMBER MATERN: Dieter Matern. So I think, what you will -- what, one of the things we discussed yesterday was that you actually say that the population that should be studied should be large enough to pick up one case based on the

knowledge we have about the prevalence of the disease in that population.

But for the test to be clinically validated, I think it is totally sufficient to have some samples from actual patients that you throw into that study, blinded, and expect them to find them, after unblinding yourself or by doing the testing.

And that should be true positives, any kind of variant of the disease you're interested in, if you have those available, to make sure that you can identify them, and you realize what you can't identify.

And then the other study will identify patients that we may not have considered because we didn't know there are extremely milder variants, or we pick up carriers, pseudo-deficiency and all those other kind of stuff when it comes to LSDs.

MEMBER SCOTT: I think it's the difference between validating the test and doing the population-based evaluation of doing this in your population.

MEMBER KELM: Well yet we're trying to figure out false positives and stuff like that, so that's where you get, you need those number from populations. Then you won't get so much --

MEMBER BOTKIN: Okay, so would that, would the edit then, of this first sentence really try to move away from the validation of the test, per se, and move towards the validation of the screening paradigm, or some other language that wouldn't be purely test-specific?

Now if we really do want to know how many false positives that were variants that you identify within the population. And that piece of it's going to be necessary, whether or not you actually identify a true positive.

DR. COMEAU: Just, to some extent, for -- and for some of our analytes, finding those false positives is going to give you more information than finding the true positive.

And so if you know that you can find the true positive, that's one thing. But if being able to distinguish, for instance, a heterozygote from

a homozygote, and knowing that your test is good enough to make that distinction, is going to tell you that the ones who are more frequent, the heterozygotes, you can distinguish them from the homozygotes.

And I think that for every different type of analyte, the test is going to be a little bit different. I think you have to be able to demonstrate, as Dieter said, that your test can find that affected newborn.

And that's the clinical validity of the test. And the clinical validity of the test within a population, I don't know that that should be a criterion for putting into Evidence Review, and whether or not it should even be a criterion -- well, I guess it has to be a criterion, to some extent, for population-based screening.

But then you're really at the whim of the frequency of the disease in the population. And if you're going to do that, then you have to consider whether or not you want to put a frequency of a disease in a population into your requirements.

DR. BAKER: Yes, actually I think they haven't standardized the nomenclature for how you define the assay validation process, also the clinical validity.

And I agree with, Anne and Dieter were talking about the clinical validity is you have a true clinical specimen and then to submit a -- going through the process, you really can correctly identify.

But also I think it's important that you have information like, I think Jeffrey was saying that you're putting the system and you have a 50 report positive, but you didn't see one, two positive. How you know this process?

But I think the decisions have to made, what you want. But one thing I want to bring in is, the analyzing of this thing. For example, charter assay, you intended to do the classic SCID, but for Wisconsin, the first case we found is not a classic SCID, it's a RAG-2 mutation.

But I think it's valid. The reason is, the -- you want to identify, and this case is truly

-- I think this case can be used like, utilized as say yes, we have evidence the process does work.

DR. TARINI: Beth Tarini, AAP. A question that goes back to this issue of pilot study research and gets to feasibility, if the pilot project study process is done using a test that is not FDA approved, so the FDA, NIH, to comment on this, does this require consent in a special way beyond opt out?

Does it require active/active informed consent? Because this could be an issue, depending on where the state of the test is.

MEMBER BOTKIN: Well, the FDA -- if it is an FDA regulated trial, then the FDA does not have waiver criteria for informed consent. SACHRP has recommended that there might be circumstances in which FDA ought to think about that, but that hasn't happened yet.

So I think that that might well complicate the situation if the FDA is actively involved in a study. I don't know, Kellie, if you have a different thought on that.

MEMBER KELM: Yes. Our regulate -- he said it correctly. So our regulations say that -- and unfortunately, it's hard to change regulations. And yes, if you have an investigational product that you're using in your test, you should have informed consent when you're using that to --

Now, if you're doing a retrospective study it, you know, most of the time that's what we have, then no, we actually have a, basically a statement of enforcement of discretion in those cases.

Because that's not just done for the newborn screening, that's almost every chemistry test is validated in that way, and when they're de-identified, you know, we obviously see no issue. It's the identification that's, you know, the information being provided that's of concern.

So, we don't know. Common law could change it, not just for newborn screening but for lots of other tests that, testing that's being done.

DR. TARINI: Beth Tarini, AAP. So

currently, then, if I were tomorrow to start a pilot study process, project, for a test or a disease using a test that is not FDA validated, or it is not FDA approved, do -- in the population, do I need informed consent?

MEMBER KELM: So here's the wrinkle of the LDT guidance, which is draft right now and not final. So, if you have a, an LDT that you have already validated, and you are, you say that it's ready to go, then, I mean, that it's not investigational anymore then, you know, similar to other ones, I mean, people have been marketing LDTs, and we've been providing enforcement discretion to those.

So obviously the difference is for a product that is not an LDT, so re-agency kits that cross interstate commerce, in that case, you know, that's not an LDT.

And then, if they're investigational, then they would need to have informed consent if they're being used where results are being provided to the physician or to the patient, until they are

cleared or approved by us.

So, but that's why a lot, most of the studies that we see tend to be de-identified samples, because it's easier for them.

CHAIRPERSON BOCCHINI: Thank you very much. All right, this third presentation is from the Timeliness Workgroup. And Kellie Kelm and Cathy Wicklund lead that workgroup.

MEMBER KELM: So, Cathy and I are co-chairing a new workgroup which we call Timeliness 2.0, because we sort of, the product of the first group is the report, which although we're -- Susan and I try to find time to actually winnow it down and publish it, that's a whole another deal.

You know, we formed a new workgroup because I think after we had our recommendations we, you know, there was some interest in the Committee in answering some additional questions, we're moving on.

So we had our first meeting yesterday, and we're still sort of putting together our` final roster. So we've had a number of people we've

reached out to. Some people apparently didn't know that we reach out, but they were there.

So we tried to enter discussions. We tried to figure out some, reach outside of our lab group and seek out people, both involved earlier, so we had some people from the nurses' side. We're trying to get in touch from people from the Hospital Association.

We are trying to involve somebody from Joint Commission, and then somebody on the, people on the other end, so specialists, geneticists, pediatricians, follow-up program participants, and then also we're going to start potentially getting into IT, communication, how communication happens down the line.

So you can see that we have quite a variety of people here with some different parts of the newborn screening process.

And I wanted to remind everybody, this was the recommendations from our committee, the final ones for timely newborn screening. And I think we've sort of talked a little bit about them,

and I just want to remind them.

So this was, you know, the first Timeliness 1.0 group really focused on a lot of the lab perspective although, I think, the collection and transit touched on some other ones.

But in order to improve those, you know, we needed more people to help us, that was sort of outside of our abilities within that, the time frame of that project.

So -- go ahead, Cathy.

MEMBER WICKLUND: Sure. Okay, so this charge was developed by a small group of individuals just to try to get our heads wrapped around some of the things that we might be able to tackle with this group. And it was really based on the outcomes of the first timeliness report.

So you can see the charge is to optimize successful strategies to address newborn screening specimen collection and transport, collect and disseminate timeliness-specific practices from state newborn screening programs, including programs that have implemented efficiencies in

collection, transport, screening and follow-up, and investigate strategies for improved standardization of communication of newborn screening results to providers and families.

One of the things, though, that we really want to be careful is, is that what else is happening in the timeliness world right now. And so, part of, I think, our job as a committee is to look critically at all of the other projects that are going on, and make sure that we're not duplicating efforts, and thinking about where the gaps might be and where we can maybe help or push things along.

So one of the things that we did yesterday, which was to get some better updates about what's happening with the CoIIN initiative, the recent newly awarded grant NewSTEPs 360, also the project that Dr. Tarini's doing on modeling and cost analysis of newborn screening timeliness, and also we heard from Dr. McCabe about the March of Dimes Newborn Screening Quality Improvement Workgroup.

So, you know, I think yesterday we had a short meeting, so a lot of it was just trying to get our heads wrapped around of everything that was happening in this space already.

The NewSTEPs 360, the proposals or the RFPs are going to be out in mid-September, and there's five different focus areas.

And I think one thing that we're thinking about is what are they going to get from the states and what they're going to be focusing on, and are there any gaps maybe, where they're not applying for all the different focus areas, and is that something that we can try to tackle?

Or, you know, so we're kind of still in, just trying to think about where we're going to best fit in.

So a lot of it was just updates. And then we started brainstorming a little bit. Did you want to add something, Kellie?

MEMBER KELM: No.

MEMBER WICKLUND: Okay. We started a little bit brainstorming on the different

projects that the workgroup could do. One of the first things we kind of honed in was the last bullet point, which was improved standardization of communication of screening results to providers and families.

And I think also what we're trying to do is make sure that we don't jump in and solve a problem that doesn't exist. So one of the first things is to like, do we have enough data that was collected from the first timeliness workgroup, or can we -- are we identifying areas where we might need more data to help us decide first if there's a problem?

So, you know, it might be that we collect data first in this area, and then see what we can do to try to, you know, help or what our workgroup could contribute to. So this was one of the areas that we thought of, might have some potential.

Another one is just in the specimen collection on the hospital side of things, and getting more granular on what's actually happening in the hospital, the relationship between the blood

draw, when that's done, but also the relationship between when a courier might come and pick that up, and, you know, what's really happening, and do we have enough data to say what's happening in that process, too?

And obviously, we had a lot of discussion, too, in thinking about standardization and what is the ability of this committee to provide guidelines, or how can we work with other groups, you know, JCAHO and other groups that actually have maybe more authority in this space than what we might have in this space.

So, that was kind of where we ended with our conversation. We didn't have a lot of time to discuss some of the potential projects that we want to tackle. Do you want to -- okay.

And so we just put our charge back up again to remind -- and again, I think it's, the big thing with our group, really is, there's a lot of work in this area, and we really want to make sure that we're going to be able to contribute in a meaningful way, and also not try to solve a problem

that doesn't exist, so -- and make sure we're, understand what the problems really are, so.

Anybody on, in the group want to add to that, that was in the committee? Oh yes, Steve?

MEMBER MCDONOUGH: Yes, I --

DR. ZUCKERMAN: Alan Zuckerman. I just wanted to raise three interesting best practices that were mentioned yesterday, one of which, the possibility of localizing ACT sheets to include contact information, the importance of documenting who has been notified and when, so that parents know which specialists or other individuals have been notified.

The importance of including communication between the hospital and primary care as well as the laboratory and other individuals, and the kind of open issue of whether point of care testing may come under this group, or if it would focus only on the lab.

MEMBER WICKLUND: Steven?

MEMBER MCDONOUGH: Yes, in conjunction with our discussions and Debi's

interest in expanding the committee, bringing other people in that perhaps JCAHO could be asked to be one of the members of our liaison, since four million babies are tested in hospitals, and they have considerable influence in how hospitals do things, that that would be nice to see if that could happen.

MEMBER KELM: So at this point we're planning, I think, monthly calls. So I think we're going to obviously need to hone in, pinpoint some projects, whether or not that's going to need to start with data collection on our own or with, for example, NewSTEPs, and then figure out some, you know, within our group, some projects that we can work on. So we're still beginning. Okay.

CHAIRPERSON BOCCHINI: Thank you both very much. Sounds like they're on their way. All right, so that leaves us with new business. So are there any issues or other business that the Committee members would like to bring forward at this time, for us to consider for future? Dieter?

MEMBER MATERN: Dieter Matern.

Given the earlier discussion about removing conditions from the RUSP, I think a first start might be to test the waters if anyone actually wants to do it is by giving them the option of adding a link on the ACHDNC website, just below the Nominate, to also, the option to also upgrade a condition from secondary to primary target, to downgrade from primary to secondary target and to actually just remove the condition from the RUSP and then see what happens.

It might force us to deal with the system, and come up with some process to do that. And then the other thing that I find interesting when it comes to the lysosomal storage disorders and how this goes about in the states, that there's one condition that is always added, and nobody ever proposed it, at least not here, and that is Gaucher disease.

And I just wonder whether at some point we just want to propose it ourselves to see whether it actually passes muster and should be included in the RUSP.

CHAIRPERSON BOCCHINI: All right, thank you. I think those are things that we certainly can look into. And I think part of the, when these workgroups are done and we're back to the subcommittees, some of these issues could easily be brought to individual subcommittees for discussion and development of recommendation to come back to the full Committee. Andrea?

MEMBER WILLIAMS: I just have a question. So are these working groups going to continue concurrently with the subcommittees? Will the subcommittees come back and then they'll have some concurrent work?

CHAIRPERSON BOCCHINI: Well we're hoping that the -- so the Pilot Study Workgroup, which may want to change its name now, may -- we hope to have the final report at the February meeting, and that'll sunset.

I think the only workgroup that will continue is the Timeliness one. That, we feel, will be a permanent, but the others will sunset. And the expectation is that by February, the

subcommittees will be back in full action. Natasha?

MS. BONHOMME: Great, thank you. Natasha Bonhomme, Genetic Alliance. So I was looking at some of the past agendas of this meeting because, you know, a lot to be learned from in that.

But I was looking, and I have to say, I'm very impressed with all the different items that this committee has tackled over the past several years, whether it's data collection, CPT code, sequencing, ACA, electronic health records, HIT, as well as the detail of, the technical details that this committee goes into.

But there is really a kind of glaring gap in that. There hasn't -- this committee as a whole hasn't had anything on its agenda regarding education since 2013.

And so it's been two years since this committee has had the opportunity to really speak in depth about education. And I'm talking about public education, health care provider education, you know, either of those, any of those, but really

have, hasn't had that opportunity to speak in depth about this.

And even though it is something that we always see on slide sets, it's always that bullet point or that sub bullet point of education, but there really hasn't been an opportunity to have an in depth discussion about this.

Even though in the past two years, there have been quite a bit of projects, both at the federal level, state level, around education, I think people really, on the ground are trying to figure out what to do, but that hasn't really been reflected on the agenda of this committee.

You know, we have work around prenatal education, around newborn screening and blood spots, the work that states have done. There's just a lot going on, that just hasn't really been highlighted at this level.

And so I really think that it would be great to be able to have the, not just one agenda, but the agendas moving forward really be able to reflect that, since it is something that, in

conversation, always kind of bubbles up, and we say, we really should do something about it.

I think this could be a really great, a platform to have the discussion around, well what is really working? What are the gaps? How do we really dig deeper? What are the lessons learned and how do we share that?

So I really encourage this committee to look at that, because earlier, the word trust came up. And you really can't have trust with the public without actually engaging in those conversations.

CHAIRPERSON BOCCHINI: Thank you. That's a good point, and we certainly should look at that, and see how we can update and bring that forward on an upcoming meeting agenda. Thanks. All right. Additional things? Dr. Botkins.

DR. BOTKINS: Yes, I just wanted to get in that issue on the radar. Aaron Goldenberg and Beth Tarini talked a little bit about this as a possible NIH grant target for this topic, but we'll see how, whether that develops or not.

But the notion is, looking at the ethics

of multiplex screening platforms. And I think it's been a long standing issue where if you have conditions that may be your primary target for which you've got good data, and you're justifying a screening for that but that comes along with a variety of other conditions, perhaps for which you have relatively little data.

And then the question becomes, can you not look at those conditions? Can you gate your machine as, so as to not to generate the data? If you do generate the data, is there an ethical obligation to disclose that, even though you may not have condition-specific, met condition-specific criteria for the RUSP, et cetera.

So that, I think, particularly as we may be moving in some context towards DNA-based platforms, that this issue of multiplexing is going to become a bigger and bigger one in newborn screening.

So, I don't know that there's a particular role for the Committee on that, but I think we are, sort of based on our organization,

sort of locked into a condition by condition review process.

But we might well think about whether there's maybe opportunities in the future to look at platforms, packages, of conditions that all share some attribute, notably the testing platform, and what the implications are of the platform for how we conduct the work.

CHAIRPERSON BOCCHINI: All right, thank you. Carol?

DR. GREENE: All great ideas so far that I would love to see taken up by the Committee and to add to the wealth. A little bit ago one of the -- at the other microphone, one of the parent group advocates mentioned that this is -- the committee, Advisory Committee on Heritable Disorders in Children.

In the last few days there's so much going on with newborn screening that really needs to be dealt with, and there are so many other disorders. And we actually had a workgroup working on thinking about how to address some of the issues,

focusing on newborn screening these -- we did a lot of work on the access to therapy and focus on newborn screening.

We're not talking about NF. We're not talking about Down's. We're not talking about any chromosomal abnormality, Fragile X, accepting so far as will it come on the screen at some point.

So I would also like to see some attention to the congenital, the heritable disorders that are not on the screen.

CHAIRPERSON BOCCHINI: Cathy?

MEMBER WICKLUND: Okay. Don't hurt me, anyone. I always have to say this, because of -- and I think it's so hard to ignore what's happening in the prenatal world, with carrier screening and everything that's happening with NIPT, and I just, I know that we're not the -- I know.

But, it just seems hard to like ignore what's happening in the prenatal world with screening and pregnant women while we're talking about things like Fragile X, Down's syndrome and some of these other things, so I know. I'm saying

it again.

CHAIRPERSON BOCCHINI: Okay. Thank you.

MEMBER WILLIAMS: I would just want to say, along that line, I'm right there with you on that. And also, Natasha, because I think this, the education and how we as families, you know, if someone can tell me in this prenatal period, or someone can, you know, address the, my need to know, not just what's happening but the truth of what's going on in newborn screening and beyond. So thank you for your comments.

CHAIRPERSON BOCCHINI: Melissa?

MEMBER PARISI: Melissa Parisi, NIH. I just wanted to circle back to this topic of outcomes and how we can assess whether or not what is being added to the RUSP is actually improving health outcomes for those individuals impacted, and if there might be a way to, I don't know whether it's a committee activity, or at least some way to try to coordinate and integrate between the various follow-up activities that are being supported by a

variety of different groups around the table, and perhaps outside, so that we can try to get at those data, because I think they're really critical, moving forward in the future.

CHAIRPERSON BOCCHINI: I agree. I think that's an important topic for us. But certainly, in the back of my mind it's highlighted that I think that with Coleen's comments with the NewSTEPs work, and with the translational network and repository, I think that this is a time to kind of put everything together as a group and kind of see where the gaps are and how to kind of figure out how to get that data in a timely fashion.

So I think that's a great suggestion. Thank you. Yes?

DR. OSTRANDER: Bob Ostrander, Family Physicians. Just a tail on the end of that, actually a lot of that outcome's concern was what the Follow-up and Treatment Workgroup was working in just before this kind of pause here.

We worked out a -- we started to work out a matrix that just tried to put certain conditions

in to see if folks are getting their recommended treatments.

I think we used sickle disease as kind of our template. So I'm looking forward to being, back on the board with the Follow-up and Treatment Subcommittee. And I think that that would be a reasonable charge to that subcommittee, as we get that going, to look at the outcome side of things.

DR. FEUCHTBAUM: Lisa Feuchtbaum, California Department of Public Health. I just want to second what Melissa just said, and many others have said, about the need for the data, basically, to measure the impact of newborn screening.

And I just want to acknowledge that California has been collecting data systematically. We have a lot of data that needs to be curated at this point.

And so it's my hope, in the next year, to really start getting some of that data out, starting with some abstracts that will be submitted to APHL, and building a team of people at the Genetic

Disease Screening Program that are really just going to try to really focus on kind of mining all of that data that we've been collecting.

And I did want to basically put a plug in for that Follow-up and Treatment Subcommittee. If that is going to have a life in the future, I think there should be also a focus on, now that we're dealing with late onset diseases, we have a lot of challenges.

How are we going to collect that data? How long is going to take? And so we're in the process of designing ALD screening in California. And this is like the issue I have to deal with next week, as we're designing our computer system.

And the issue is, what is that long term follow-up going to look like? And so anyway, we'll go ahead and design the data collection screen, or data collection form, if you want to think of it that way.

We're going to harmonize it with what New York is doing. And -- but then there's the technical part. How many years do we need to go

out? Because we only go to five years now. Obviously we're going to need, maybe, to go to 18 years, and should we do, be doing that with the other diseases as well?

There's only so much you can learn about in five years, so. Anyway, any efforts to support states to collect that kind of data, I just highly support. Thank you.

CHAIRPERSON BOCCHINI: Other questions, comments? All right, if not, we've come to the end of the agenda, and I certainly want to thank committee members for all of their work, and all of the people who have come to the microphone, the liaisons, for their comments and input.

I think this has been a very valuable meeting, and I appreciate all of the work that everybody's done to m Gake it happen. I'll highlight Debi Sarkar and the work that she's done to kind of keep things organized, and to reiterate to HRSA that this onsite venue has worked out really well.

So we appreciate it. Just to let you

know that having us all in the same room has worked very nicely. Thank you. So that'll conclude the meeting.

(Whereupon, the meeting in the above-entitled matter was concluded at 12:22 p.m.)