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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THURSDAY
AUGUST 27, 2015

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The Committee met on the Terrace Level, 5635 Fishers Lane, Rockville, Maryland, at 8:30 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
DEBBIE BADAWI, Association of Maternal and Child Health*
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, LTC 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
MICHAEL WATSON, American College of Medical Genetics & Genomics

*-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

(8:37 a.m.)

CHAIRPERSON BOCCHINI: All right, good morning everyone. I'd like to welcome you to the August meeting of the Advisory Committee on Heritable Disorders in Newborns and Children. This is our second meeting of our, of this Committee. And it is a Webinar and so we're happy to be here at this site with all of you here and with people on the line.

I have some opening remarks for everyone. I'd like to introduce two individuals. We have a new ex officio member for representing AHRQ, Dr. Kamila Mistry. Kamila is not here at the moment. And then the new organizational representative for ACOG, Dr. Joseph Biggio. Welcome, happy to have you here.

And so we'll start the meeting with a roll call. So we'll go through Committee Members first. Don Bailey.

MEMBER BAILEY: Here.

CHAIRPERSON BOCCHINI: Here, Jeff

Botkin.

MEMBER BOTKIN: Here.

CHAIRPERSON BOCCHINI: Coleen Boyle.

MEMBER BOYLE: Here.

CHAIRPERSON BOCCHINI: And then representing NIH this morning is Tiina Urv.

MEMBER URV: Here.

CHAIRPERSON BOCCHINI: Kelly Kelm.

MEMBER KELM: Here.

CHAIRPERSON BOCCHINI: Fred Lorey.

MEMBER LOREY: Here.

CHAIRPERSON BOCCHINI: Dieter Matern.

MEMBER MATERN: Here.

CHAIRPERSON BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: Here.

CHAIRPERSON BOCCHINI: Joan Scott, representing HRSA.

MEMBER SCOTT: Here.

CHAIRPERSON BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Here.

CHAIRPERSON BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Here.

CHAIRPERSON BOCCHINI: Andrea Williams.

MEMBER WILLIAMS: Here.

CHAIRPERSON BOCCHINI: And Debi Sarkar.

MS. SARKAR: Here.

CHAIRPERSON BOCCHINI: And then organization representatives in attendance.

Freddy Chen.

DR. CHEN: Here.

CHAIRPERSON BOCCHINI: Beth Tarini.

DR. TARINI: Here.

CHAIRPERSON BOCCHINI: Mike Watson.

DR. WATSON: Here.

CHAIRPERSON BOCCHINI: Joseph Biggio.

DR. BIGGIO: Here.

CHAIRPERSON BOCCHINI: And then on the telephone we have Debbie Badawi.

DR. BADAWI: Here.

CHAIRPERSON BOCCHINI: And Susan Tanksley.

DR. TANKSLEY: Here.

CHAIRPERSON BOCCHINI: Chris Kus is also on the phone. Chris?

DR. KUS: Here.

CHAIRPERSON BOCCHINI: All right and then also on the phone should be Adam Kanis.

DR. KANIS: Here.

CHAIRPERSON BOCCHINI: Natasha Bonhomme.

MS. BONHOMME: Here.

CHAIRPERSON BOCCHINI: Ed McCabe.

DR. MCCABE: Here.

CHAIRPERSON BOCCHINI: And then Cate Walsh Vockley.

DR. VOCKLEY: Here.

CHAIRPERSON BOCCHINI: And Carol Greene.

DR. GREENE: Here.

CHAIRPERSON BOCCHINI: All right. Thank you all.

Next slide.

So just to review what happened in the interim from our last meeting. We did send correspondence to the Secretary on our timeliness recommendations, and the recommendations include MPS1 on the RUSP.

The Secretary acknowledged receipt of the timeliness recommendations. And the MPS1 recommendation is currently under review with the Department.

We also sent a letter from the Committee to the Secretary on our support of the recommendations for Newborn Screening Form consent. And we have not yet received a response from the Secretary from that correspondence.

Next slide.

So as you know at the last meeting we decided to reset our priorities to address the issues that were raised in the re-authorization of our Committee. And as such, we have focused our activities on three work groups.

One is the Pilot Study Work Group which

was already under way. And then we developed a Cost Analysis Work Group. And then because of the requirement that we become involved with addressing issues of timeliness, we formed, continued that work with the development of a work group.

These work groups will meet later today. The meetings of the work group are closed but we will have summaries of the activities and discussions with those work groups presented in tomorrow's meeting.

And then lastly, our goal is to also determine what essential elements we need for the nomination of a condition, so that we can meet the nine month deadline from the time that we turn a condition over to the Condition Review Work Group for its evidence review, to the time that we as a Committee need to make a decision. And so that is a process that's ongoing as well.

Next slide.

And it doesn't mean that the subcommittees that we have don't continue to exist.

They've just been suspended for a short period of time while we meet these priorities. And in our February meeting which will be another in person meeting, the subcommittees will meet.

At that point we hope to have information related to the priorities work. And then ask those subcommittees to then look at potential projects to bring forward to the full Committee for evaluation based on the priorities and the needs that are identified because of the work of the priority work groups.

These will be finalized by the full Committee, prioritized by the full Committee, and obviously the goal then is to address what needs and gaps that have been identified within the scope of work of the Committee.

Next slide.

And then just for your calendars, moving forward as you know, we've been authorized to have four meetings a year. At this point in time they are not all in person meetings. And so that as you can see, some are Webinars. Some are

Webcast in person. We're on our third meeting of 2015. The next meeting will be a Webinar in November. And then the four meetings that are scheduled for calendar year 2016 are listed on this slide.

Next slide.

So just a quick review of today and tomorrow's meeting. We're going to start with a report from NewSTEPs on the state of Newborn Screening in the United States. Very importantly, we'll have the final evidence review report on for X-linked adrenoleukodystrophy. And the completion of that evidence review and discussion by the Committee. There will be a vote on whether to include ALD on the RUSP.

On day two -- and then following that the work groups will meet this afternoon. On day two we'll have summaries of the work group meetings and then hear an update on the implementation of SCID, critical conditional heart disease, and Pompe disease.

Next slide.

I'm going to turn this over to Debi for a couple of additional comments about the Committee and conflict of interest and some housekeeping.

MS. SARKAR: Hi, everyone. My name is Debi Sarkar, I am the designated federal official for this Advisory Committee. So I just wanted to go over a few things.

First we have three openings that are coming up next year for this committee. We had a solicitation, and we asked for nominations to fill those openings. We had, we received many nominations and all were very highly qualified. And I think the decision will be hard to just pick through.

But the clearance process has started and it will take about a year to find out who those three people will be to fill those spots. We expect that the terms will begin in or around July 2016.

Also I know several of the organizational representatives have asked about their terms. Actually what Dr. Bocchini and I have

been talking about is we'd really like to see if we can include more organizations. But this might entail us having to update the Committee's bylaws.

So for this meeting we're going to just continue as is. And by November we will have more information about the organizational representatives. I can say right now that we don't want to lose anyone that we have right now. So just want to have more.

So next, by now the Committee, you all have heard me say this many, many times but I have to say it again, we do have an important vote coming up. So I just wanted to remind everyone that if you have any inquiries due to your position on the Committee, to please let Dr. Bocchini or I know prior to committing to answering those questions.

I just want to remind everyone again that you must recuse yourself from participation in all particular matters likely to affect the financial interest of any organization with which you serve as an officer, director, trustee, or general partner unless you are also an employee of

the organization. Or unless you have received a waiver from HHS authorizing your participation.

So in other words, when a vote is scheduled or an activity is proposed, and you have a question about the potential conflict of interest, please let me know immediately.

Before we get to the May meeting minutes I just wanted to go over a few housekeeping items. Just to make everyone aware this meeting is being Webcasted. This is the first for me, which means people on the internet will be able to see everyone here. And they'll be able to see the meeting deliberations. So just FYI.

And then I also again ask whenever you are speaking to please identify yourself and we do have a transcriptionist here who is recording everything. People on line who are viewing, we all know that the Committee Members are famous, but it would be helpful if you could tell us who you are.

And the last but probably most important, bathrooms are down through the glass doors. Go past the elevators to your left. Food

is upstairs. There's a Sprout Cafe where you can get food and drinks. That is all for me.

CHAIRPERSON BOCCHINI: Thank you, Debi. So next on the agenda is approval of the minutes from the May meeting. Each of you Committee Members have received the copy of the minutes in the agenda book. And so we'll vote to approve the minutes of the meeting.

First are there any additions or corrections to be made to the minutes as they were distributed? Yes.

DR. TANKSLEY: Correction one --

CHAIRPERSON BOCCHINI: Sorry, you need to be on the microphone.

DR. TANKSLEY: I just has a couple corrections one was a date and the other was --

CHAIRPERSON BOCCHINI: Turn on the microphone.

DR. TANKSLEY: Now it's on, can you hear me now? No?

Now you can hear me. So one more time. Susan Tanksley, one is a correction of a date, the

other is a correction of initials from our organization.

CHAIRPERSON BOCCHINI: Okay. That's good, okay. Any other additions or corrections?

(No audible response)

CHAIRPERSON BOCCHINI: All right hearing none we'll go ahead -- Yes, Dieter.

MEMBER MATERN: I sent you a file with some minor typing errors and stuff.

CHAIRPERSON BOCCHINI: Okay, thank you.

All right. Cathy.

MEMBER WICKLUND: I don't see my name listed as being there, on the 11th.

CHAIRPERSON BOCCHINI: Well that would be a serious error.

MEMBER WICKLUND: Wasn't I there?

(Laughter)

CHAIRPERSON BOCCHINI: All right.

MEMBER WICKLUND: Oh, this was the one on the phone. Oh, sorry. I was not there.

(Laughter)

CHAIRPERSON BOCCHINI: You take that back. Okay, all right. Other comments?

(No audible response)

CHAIRPERSON BOCCHINI: All right, hearing none we'll go through a voice vote.

Don Bailey, approve?

MEMBER BAILEY: I approve.

CHAIRPERSON BOCCHINI: Jeff Botkin.

MEMBER BOTKIN: I approve.

CHAIRPERSON BOCCHINI: Coleen Boyle.

MEMBER BOYLE: Approve.

CHAIRPERSON BOCCHINI: Tiina Urv.

MEMBER URV: Approved.

CHAIRPERSON BOCCHINI: Kellie Kelm.

MEMBER KELM: Approve.

CHAIRPERSON BOCCHINI: Fred Lorey. Know Fred is? Okay.

CHAIRPERSON BOCCHINI: Dieter Matern.

MEMBER MATERN: Approve.

CHAIRPERSON BOCCHINI: Steve McDonough.

MEMBER MCDONOUGH: Approve.

CHAIRPERSON BOCCHINI: Kamila Mistry.

MEMBER MISTRY: Approve.

CHAIRPERSON BOCCHINI: Joan Scott.

MEMBER SCOTT: Approve.

CHAIRPERSON BOCCHINI: Alexis Thompson.

MEMBER THOMPSON: Approve.

CHAIRPERSON BOCCHINI: Cathy Wicklund.

MEMBER WICKLUND: Approve.

CHAIRPERSON BOCCHINI: And Andrea Williams.

MEMBER WILLIAMS: Approve.

CHAIRPERSON BOCCHINI: So the minutes of the meeting are approved with the suggested changes that were made through the Committee.

All right the first presentation today is by Marci Sontag. Marci is the Associate Director of NewSTEPs, and Assistant Professor of Epidemiology in the Colorado School of Public Health. She's worked in newborn screening since 1995 with significant experience in cystic

fibrosis specific activity.

Dr. Sontag holds a Master of Science in Biostatistics and a PhD in Epidemiology.

This morning she's going to talk about NewSTEPs data repository, the state of newborn screening in the United States. Marcy.

DR. SONTAG: Thank you. Thank you Dr. Bocchini and Debi for inviting us to speak today on NewSTEPs and the state of newborn screening in the U.S. And also thank you Committee for giving me an extra nine minutes to be able to present what is a very full presentation that we have this morning.

I'm very honored to present this presentation on behalf of my NewSTEPs team, as well as really the newborn screening community, because this is their data.

NewSTEPs is funded as a cooperative agreement from HRSA to APHL and APHL collaborates with the Colorado School of Public Health to implement NewSTEPs. Our goal really with NewSTEPs is to provide a technical assistance and resource

center and data repository for the newborn screening system to help support newborn screening throughout the U.S.

So today I'm going to talk about the data that is available to support newborn screening in the U.S. as they work to improve their systems.

We have a NewSTEPs data repository that is really built to provide tools to newborn screening systems to help them evaluate, analyze, and benchmark their programs.

The components of the data repository we divided across three different groups of information. State profiles which includes the demographic information and the basic information about state policies. Case definitions, information about individual babies identified by newborn screening, and equality indicators. And I will talk about each of those in a little bit of detail.

If you want more information about your favorite states, I encourage you to go to our website at NewSTEPs.org. Click on your state and

you can find a lot of information about your state and their individual policies.

The data collection and confirmation are within our data repository. It was built over really several years. We were working a vendor 5AM Solutions to build this repository, and partnered with many members of the newborn screening community to develop the elements within the repository.

To populate this repository, it's not everyone's most favorite job to enter data into a repository much to our chagrin. So when we ask people to enter data it's hard to find that time. And yet we found that if we called and interview them, and say hey, tell me about your program, they'll spend that hour of time with us to tell us about the program. We can help them to enter that data, and also use that as a time to train them on how to use the repository, using a web based format.

Following that we then had data entry from newborn screening programs, so they went back in to fill in some of the additional information.

And prior to this meeting, we had confirmation of the data via our printed summary report.

We sent the summary report that's in your briefing book, a copy of that to all of the states, told them we would be presenting that here to all of you on this Committee, and asked them to confirm that data before we submitted it.

So we got a lot of changes back and they said, oh, we had kind of reported this in a little bit, you know, not quite the right way. And they made those changes for us.

So this is an iterative process to make sure we are continuing to enter the data, correct the data, curate the data and make sure it really represents truly what state newborn screening programs are doing.

And many of you are familiar with this complex slide from Dr. Susan Tanksley from Texas, really showing all the complexities of newborn screening. As we conceptualize this at NewSTEPs, we said there are certain areas of this that we really feel are our responsibility to capture and

to report.

So we have taken this and tried to simplify it to, we used this simplified map, "simplified map", to help us move through the presentation today. And we've printed this up, displaying what's the new breast feeding process model, starting with the pre-analytic stage, and I'll walk you through each of these stages as we go through the presentation.

I'm going to talk a little bit about rules and regulations and how states think about their policies and procedures. And then the analytic, through the post-analytic stage. So I'll break these up. I don't expect you to digest this all right now.

So starting initially with the pre-analytic, the first thing we start with, start with the baby, start with that birth. So how many births do we have in the U.S.? When we talk to state newborn screening programs, most of us say we're from a small state. Many of us say that, and that's because many of us, or most of us are not

California and Texas.

So there's a lot, a lot of those states, those very large states. However, the medium size of states in this country is 52,000. So half the states are smaller than that. And there's a lot of states that are in the middle.

So 50 percent of the states have births between 21,000 and 87,000. That's still a pretty big range. So when we conceptualize how we support state newborn screening programs there are different needs for different sizes of states.

So the needs in these states up here, the states that have over 100,000 births per year may be very different than the needs here at the bottom. Those states that have less than 10 or 20,000 births per year. So we're trying to conceptualize ways that we can help support states in that manner.

In addition to that birth rates vary between states, but we know the highest birth rates happen in states such as Utah, Texas, and Alaska. And then the lower states, the lowest birth rate

states are up in New England, Oregon, Florida, and we can kind of adjust that map here.

This is important for us to think about that impact on per capita, you know how many people are living in that state versus how many births? And that definitely impacts the newborn screening program and the resources that they have.

So what, how can we help support them? One way that's already in place for many years to support newborn screening programs and our systems, are through the regional collaboratives. This is a map of the regional collaborative networks. Really divided based on geographic regions, understanding that the states in different geographic areas have different, potentially have different needs.

Including Puerto Rico there are 52 newborn screening programs. Those 52 newborn screening programs have the laboratory activities completed in 36 newborn screening labs. As there are many regional newborn screening labs that perform the testing for a state.

And you can also see there is geographically diversity. There are very large states with 663,000 square miles in Alaska, down to the smallest state of little over 1,000 square miles. So there's lots of various challenges that affect all of the things we talk about on this Committee.

That affects timeliness, access to care. Do they have those specialists available to them? And these are the types of things that at NewSTEPs we're reaching out to the states to find out what are their needs based on their various geographic challenges and the number of babies in their states.

So now we know how the babies are born, well not how they're born, but how many babies are born, that's beyond the scope of this talk. We're going to talk about the newborn screening dried blood spot collection.

And for most of my talk today, I am going to talk about dried blood spot collection and what we know about that. That's not to distance the

point of care testing. We're going to talk a little bit more about CCHD specifically tomorrow.

The dried blood spot collection beginning at consent, storage, and timing of collection in this next section. So to talk about consent, I'd like to point you to work that has been done and funded out of the Heartland Regional Collaborative. This was done by Jeremy Penn from North Dakota.

And he did a great survey of all states and the District of Columbia to find out about their refusal. Why they refuse, or what are the mechanisms that they allow refusals of newborn screening. And we have much of this data in our data repository as well, but he went into a little more detail that I'd like to point out here.

So we know that consent is implied in those states. Most babies get newborn screening through an implied consent model, but most states also allow parents to opt out of newborn screening for religious reasons, or for other reasons.

There are no provisions for refusals

here. You can see in three states. I would really encourage you to dig down a little deeper in his work. I think we sent this link in our, within your briefing book, within our slides. If not, please take note of it because there's a lot of information that's about the consent in everyone's screening programs.

We talk about consent to screen, but then also what do we do with those, the data and the samples after we have collected them. And the consent process there.

Well first dried blood spot retention time. And this is dated directly out of our NewSTEPs repository. How long are states storing data? This is a heat map where the lightest colors here are states who store the data for the least amount of time. In this case represented by one to six months. Up through the darkest states who are storing data for 21 to 30 years or indefinitely.

You can see there's quite a range here of how long states are storing, I think I said data, this their dried blood spots. This is dried blood

spot retention. How long are they storing those dried blood spots?

Some are storing them just long enough to be able to confirm abnormal tests if needed and then they're being destroyed. And some are storing them indefinitely. And we'll get into that indefinitely and consent in a minute.

And what about data storage? So don't often think about how long do you store your data, but this is a very important issue for state newborn screening programs.

So on the left we're displaying the normal specimen data storage period. How long are people storing their data from normal newborn screening results? And on the right is the abnormal. Now the red states here are those states who don't have a data retention policy. There's nothing officially on the books in those states that are referring to a data retention policy.

Then you see in both instances here that the lighter colors are the shorter time periods, storing their data for two years or less. Up

through the darker time periods, those were storing their data for 20 years or more.

And there's a lot of implications here for data storage, data access, who has a right to come back and ask for that data? We've seen some of the challenges that Beth Tarini has brought forward with the sickle cell and the, I can't remember the name, but college organization that is looking out for students, NCAA, thank you. I was coming up with NAACP.

This is going to be an audience participation time. The NCAA asking for all students to be tested for sickle cell disorder, and people reaching back out to the state newborn screening programs and Beth did a great job thinking of the burden that that would potentially put on state newborn screening programs.

Yes, Coleen.

MEMBER BOYLE: Just a quick question on what the gray is? They're not provided. Is that mostly that they're -- that's not available, it's not in their policy, or?

DR. SONTAG: Yes, so on all of our maps there is some, there are some states that are gray. And those are states that haven't answered that question in our repository. So all states have answered most of the questions in our repository, but there are some states that just haven't answered a specific question. And we'll be continuing to reach out to them to get that information.

Now one of the big things we've all been talking about on newborn screening recently is the informed consent for research and storage of dried blood spots. This group is very familiar so I'm not going to go through this in detail, but the Newborn Screening Saves Lives Act brought about much more awareness that we really need to be thinking about.

Giving consent this is now, research on dried blood spots is considered human subject consent, or human subject research. And we need to get consent on these samples. So what do we know about which states are really doing research on

their newborn screening dried blood spots? So which states use dried bloods for research?

Here again, gray is those states who haven't provided information, but I want to draw your attention to the orange. Those are the states that do not typically use dried blood spots for research. And purple is states that do allow research on their dried blood spots.

All of us are thinking about what are the implications however of research on dried blood spots, I'm thinking what is research? And that's a composition that has come to this Committee and has gone to -- many of us have been involved in many conversations about the research for dried blood spots.

(Off mic comment)

DR. SONTAG: Yes and no. For those of you in the back who are not able to see that, it indicates whether residual dried blood spot specimens are consented for research. And that's based on historical policies. And now with the new, Newborn Screening Saves Lives Act that is

going to be changing as, well just consented.

(Off mic comment)

DR. SONTAG: Oh, no, no. Jeff Botkin says no, no.

MEMBER BOTKIN: Well no, maybe I'm confused, I thought this was what state policy was about, whether there is access to the spots, not necessarily whether there's consent for --

DR. SONTAG: Yes, so that is true. And so there are little letters on these slides that I was not going to go into the detail of, but are little letters on this map that those in the front row are able to see, that say yes or no. So the orange and purple is, orange is are they typically used for research? And the purple is -- or the orange is they are not typically used for research, purple is yes they are typically used for research.

However, you would see on some of these slides that yes or no is consent, let's see, are they consented for research? And this is what's currently in our data repository knowing that most states are going to have to go through consent for

research for newborn screening dried blood spot use.

MEMBER URV: Quick question, so is that considered research external to what the laboratory is doing, or what the state might be doing for surveillance?

DR. SONTAG: Yes, so this is very broad. Do you, from the state perspective, do you allow research on your newborn screening dried blood spots? And do you collect consent? So we haven't got into those details, and we're thinking of how to ask those questions to get into more of those details of what they do.

How do they define research? Is it QA/QC? Is it, you know that whole where do we put the, draw that line for research, is still --

MS. SARKAR: And that was Tiina Urv from NIH asking the question.

DR. SONTAG: Carol.

DR. GREENE: Hi, I think it's going to be important to say --

MS. SARKAR: That's Carol Greene.

DR. GREENE: Carol Greene, sorry. Thank you, SIMD. The comment was just made to define research, does that include QA/QC? As a definition QA/QC is not research, so it's important to --

DR. SONTAG: Excellent, yes.

DR. GREENE: -- know what states mean, but it is important from the perspective of this Committee QA/QC is not research. It's required by CLIA for a lab to keep running.

DR. SONTAG: You're absolutely right, Carol, so I did misspeak there because it is, there's the QA/QC and there's research, but there's a lot of gray in between that is really being defined right now. So where do you draw that line in the conversations are, a good point.

Okay. Timeliness for newborn screening. We've been talking a lot about newborn screening timeliness. This is the group that's developed and approved these recommendations, so I'm not going to go through the details of these recommendations, but we have been thinking a lot

about timeliness at NewSTEPs as well. And are now digging into what do we know about timeliness from the state and newborn screening perspective?

Now what I'm presenting here is not all 4 million babies. I'm presenting a snapshot of the data that we have on cases reported to the NewSTEPs data repository. These are reported cases with a disorder, diagnosed by newborn screening, from states with signed MOUs. And really this is very specifically to a few specific disorders.

We're doing this data collection for the cases in a very deliberate and thoughtful way to get specific information in kind of a pilot format so we can refine these case definitions and refine the process.

So this is about 900 cases that are represented here, and will be represented throughout the presentation. So this is a disclaimer, not all newborns or all disorders.

But for specimen collection, let me first orient you to a box and whisker plot. So for those of you not familiar with a box and whisker

plot, the middle line of the box is the median or the 50th percentile. The outside lines of the box are the, the bottom one is the 25th percentile, and the top is the 75th percentile. And then 95 percent of the data are going to fall within those whiskers.

So then these little dots up here are individual cases in which they were, those are the outliers that fall outside that 95th percentile.

So this is specimen collection. Now when we collect the specimen we know nothing about whether the baby has a disorder. So this should be representative of the other babies. Again, this is from a limited number of states. But you can see here that the median time of collection is 40 hours, a little less than 40 hours of life.

So within that 24 to 48 hour window, almost all babies the 25th and 75th percentile includes that 48 hour mark, with most being collected in that time. Some are being collected very early, and then there are some that you worry about it being collected far too late.

So this gives us a chance to really look

into which states can we help out with that specimen collection time. So we're looking very carefully at timeliness.

When we look at individual states, and I just have eight states represented here. And those names are listed, but you can see that for the most part, most states the median value is in the low 20s. Some pop up a little bit above 20, some into the 40s. But you can see that median value typically follows where we hope that it would land.

However, we see there are some babies who are being screened very late. And we don't know what's going on with those newborns. What's going, there may be something specific about that situation. Are they in the NICU, we don't know what's happening there. But we can go back and talk to some of these states and say, what's happening?

A good reminder that we have to be very careful of how we look at these data. That the median is not enough. Because the median gives us

a good feeling that, yes, we're tracking pretty well. But yet that's spread across each of these states is pretty wide.

And there's definitely some newborns that we need to, there's some states that we can hopefully provide some guidance to and figure out what -- how can we get those babies screened earlier?

Now we talked about dried blood spot collection, I want to spend a little bit of time talking about the dried blood spot shipment and the arrival at the lab, and the operating hours of the lab.

So this is a slide depicting the courier service usage status. So the green states are those that provide a courier service, the state provides a courier service for use by the birthing centers. The blood states are those that all birthing centers use a courier service.

And then orange is other. And these are people of the states that really wanted additional information. Give us additional information

about their courier service use. And most of those orange states are also states that are implementing a courier service as well. And had some specific detail about that courier service.

Question?

DR. TARINI: Beth Tarini, AAP. Quick question which my understanding is from some representatives, when you say courier, does that mean a private transport service? Or does that refer to FedEx, UPS? The difference being in the later, you are constrained by their schedule. And in the former, you can request and pay for a specialized schedule?

DR. SONTAG: Yes, that's an excellent question. And this represents both of those were lumped into the same bucket. So this map here, we have some that additional data but this map here represents any FedEx or private couriers for this.

One thing of note. If we were to have presented this same map five years ago there would be very, many fewer states who were using a courier service. So this is something that has really

changed over time.

And I can't represent every state here, and those who've changed policies recently, but I want to highlight that Tennessee has changed their policies for delivery of samples.

Made the news recently, and really threw a series or a -- yes, a series of rolling out how they're getting courier services to different regions of their state. First to one region, then another region, then another region. They are really providing courier service now to most of their state, so that all of those samples are getting into the lab in a much more timely manner.

So we can get the samples there quickly but if we're not open at the labs, it's hard for us to test the samples. So what is the weekend operating status for the newborn screening programs?

Here you see that the dark purple here on both sides. On the left side we have the states lab hours. And on the right side we have the follow-up hours. So on the left side where you see

the lab hours, the dark purple is those that are open on Saturday and Sunday.

And the orange is those that are just open on Saturday, not open on Sunday. And the lighter colors are those who do not have weekend operating hours. And you'll note on the right side, with the follow-up status that many states, there are more states who are the lighter color over here that look like they have lab hours.

The one thing that's not depicted here is that many programs have follow-up hours that are, follow-up staff that are on call. So they are not there all day on a Saturday or a Sunday, but they are on call to provide services. And that's not depicted on that map. Again, this is another thing that has changed very quickly. In large part due to the recommendations that have come out of this Committee.

I'd like to highlight some of the work in Colorado where they have expanded newborn screening to weekends. Also getting some press in Colorado and nationally. And in addition to

adding Saturday operating hours, Colorado has partnered with the Colorado Hospital Association to improve timeliness.

And in addition to that has added courier service, six day a week courier service. So they actually have couriers picking up samples on Sundays. The labs not open on Sundays, but the courier picks up on Sundays, so that the samples are all available back in the lab on Monday morning. It's kind of a creative solution to how to think about getting those samples to the lab in a very timely manner.

So these are just, Tennessee and Colorado are just two examples of state programs that are making changes to improve the timeliness of newborn screening.

And so now I'm going to talk very briefly about data entry and confirmation. This is a very big challenge for state newborn screening programs. And beyond the scope of this presentation to really go into too much detail here, but I want to talk first about the LIMS

system.

This is the Laboratory Information Management System that states used to track data as it's coming into their program. And then track the sample as it's going through their system, and the results that go out, and out to the clinicians.

So I'd encourage you if you want more detail on this or any of our other reports. Go to our website. I have on that Maps page you can click on Maps and Reports. It gets you to this page, and then you can click on various different reports that are updated automatically in the repository. You can click here on the LIM systems report, and that would pop up some other windows that gives you a summary of the LIM system.

So we have several LIM systems listed here. Of note you'd see there PerkinElmer and Neometrics/Natus are the two most commonly used LIM systems currently in laboratories. And you wanted to find out more information about your state system, you can go over here on LIM system by state. Find out what they use both for their laboratory

management, and for their follow-up management.

Now having said all that, I talked a little bit about getting that sample in and tracking it. There's a lot of challenges that states have in timely newborn screening and getting that sample in, entering the data off the dried blood spot card, making sure it's legible, getting all of the information. Because many times specific information might be missing.

That critical information to know how to contact that family again. That can absolutely delay timeliness in newborn screening. If you don't have the babies name and how to get in contact with them, it's hard to follow up, and do that follow up when you have a critical result.

So there's lots of people in this room and beyond who are thinking very carefully about how we can improve that aspect of newborn screening as well. And hopefully in the next couple of years we'll be back here and telling you some of the successes that are related to that.

Yes, ma'am.

DR. TARINI: Beth Tarini, AAP. Do we know what is the most common information piece that's missing when it arrives at the state? Is it the name, the transfusion -- I asked because in speaking with hospitals, it seems, anecdotally that their delay is something that may not be crucial to the actual processing of the card. Although the hospital believes that the card must be 100 percent complete before it goes out which just depends on what the element, the information element is.

Do we know which are the most high frequency absence elements?

DR. SONTAG: You know I don't have that data at my fingertips. I will tell you that a lot of people are asking states about that. What is the critical information? Because the critical information for one state is different than the critical information for another.

Like what they've defined as, we can't move forward without this, varies a little bit from state to state as well.

DR. TARINI: Because of the disorders or just because of their process?

DR. SONTAG: Because of the processes. Because each state has their own process and what they require on that dried blood spot card. That's a very good question.

So I want to talk a little bit about the newborn screening processes. But before we get to the lab, how do they make the decisions about what it is they're going to be screening for?

So this is related to states that are doing one or two screens. This is, we fall very strongly into the camps that we fall into whether we're a one screen state or a two screen state. And there can be very heated discussions about whether we're a one screen state or two screen states.

Here the purple states are those that are the two screen states. And the orange are those who are one screen. But the caveat that some of these, most of the purple states have mandated two screens. But states such as Washington and Wyoming, have one mandated screen and a very

strongly suggested second screen.

And in those cases, those states really function as a two screen state because they get that second screen on most of their individuals.

So I said there was two pretty strong camps as to one or two screen states. Is there a benefit to one, or is there a benefit to two? This is a really, really tough question. And Dr. Stuart Shapira along with his colleagues at CDC and the folks at APHL have tried to dig into this and get this information to understand, do we need to do one or two screens?

And it's very hard because once you start comparing the two screens to one screen, all the cutoffs are different. And what happens? So in this paper that just came out last week in Molecular Genetics and Metabolism, you'll see that the two screen states identify a lot of kids with congenital hypothyroidism on that second screen.

But if they were to change cutoffs, might they have identified all those babies on the first screen? So it's a very tricky question to

answer, and the conclusion of this paper states that two screen states might be able to convert to a single screen operation for congenital hypothyroidism, this is for CH, without loss in performance.

This doesn't touch the other disorders for which two screen states use that second screen. But this is a complex issue that I would encourage you to look at Dr. Shapira's paper.

So in addition to, one or two screen states, a very common question we get at NewSTEPs is what are the newborn screening fees across the country? What are the differences in the fees?

So this depicts the differences in the fees. The lightest colors are no fees, up to the darkest colors are the highest fees. So that heat map is representing the range of the fees.

Again, there's a lot of caveats here. I know those of you who are in states, are saying yes that's my fee, but I want you to know that -- and there's a lot of ways that states pay for screening beyond fees.

Some states are completely dependent upon the fee and fund all of their newborn screening program from those funds. Other states are using other mechanisms, general funds, other billing mechanisms to pay for newborn screening operations. So it varies from state to state.

But for those states that do utilize their fees, what are the types of things that are covered by the newborn screening fee? Here's a list, not an all-inclusive list of what is covered by a newborn screening fee. I'll let you look through it.

We're really covering program staff, it could cover courier service, running the laboratory test, follow-up services. Long list here, this is the list compiled from many different states.

And one of the most important questions I think we all think about is which states are screening for what?

DR. TARINI: Beth Tarini, AAP. We started looking at the fees, and one thing I want

to bring to the Committee's attention -- not for necessarily now especially because I'm the state representative on the Committee for the American Hospital Association for Michigan, and so I have to answer every time we raise the fees as to why is that -- when people talk about the fees, they talk about, well I use the fees to pay X. I use the fees to pay to Y, or I use other services. I think one important point to acknowledge and think about is that those states that are heavily reliant on fees, regardless of which services they pay for, have in that method of finance a potentially limited well to which they will continue to go back to. Because the fees are often paid for by the hospitals.

So near complete reliance on the fees may pose a long term problem regardless of what exact services they're paying for, unless you're going to cut those services. So just to point out that you can pay for your newborn screening program a number of different ways, but the feasibility as we grow potentially will become complicated by this

framework.

DR. SONTAG: Yes, thank you, Beth. That's an important point. And important for us to be considering as we're moving forward and to talking about with people who really understand the cost and the charges that are associated with newborn screening.

So one of the big questions we get is what are you screening for? What states are screening for what? This is the group that approves the new disorders that go on that recommended uniform screening panel. Right now there are 32 disorders on the recommended on the RUSP waiting for the approval of MPS 1. And then later today the vote for X-ALD.

But it's interesting when you ask the state, how many disorders are screened for in your state? And states could answer 45, 62, 38, how do you compare those? So at NewSTEPs we've divided this by counting the disorders as those around the core disorder, core panel, secondary panel, and the other panel. The other meaning things that aren't

recommended officially by this group, but things that states screen for.

So we really try to count primarily those that are on that core recommended uniform screening panel. Here's the recommended uniform screening panel as of March 2015. This is on the HRSA website with 32 disorders. Last one being added was Pompe.

And then we have the secondary conditions. These secondary conditions are also listed on the website and by definition, these secondary conditions are disorders that can be detected in a differential diagnosis of a core disorder.

So it's important to note here when a state is screening for something, they might identify other things through that process. It's what they say officially that they are going to be screening for. It's very important to a state newborn screening program that they put on a stamp of approval, saying we're looking for this. And we're going to do our very best to find this

disorder.

The secondary disorders, we're not putting our stamp of approval and saying yes, we guarantee we're going to find these or do our very best to find these. There's no very great guarantee, but they do our very best to find these. But if we find them, we're going to report them. So that's an important differentiation between the two.

So here's the screening of the 32 core disorders. Where you see the darkest states, so this is again another heat map showing the darkest states of those states that are screening for 32 disorders. And ranging down, until you note from this map that Illinois and New York are both screening for, currently screening for the 32 disorders that are sort of the uniform screening panel.

And there are many other states that are very close to adding that 31st and 32nd disorders. So I think we're getting pretty close here. And Jelili Ojodu will be talking more detail about

that, about some of those conditions tomorrow.

Other disorders that screened in the U.S. These are disorders that states are reporting to us at NewSTEPs. I'll let you look for your favorite disorder on this list, not going to read through them. If you want more details you can go to our website and find out, I want to know who's actually screening for this?

Now this is universally screened. This is not we're doing a pilot study, we're doing research on this. We're trying to figure out what's going on here. This is we universally screen for these disorders.

You want more information you can go to our screened conditions report. Same place that I was talking about earlier. You get to these reports and you can click on, right now, we're interested in MPS 1, one that might be added to the RUSP shortly by the Secretary.

Down here at the bottom it says MPS 1. How many universally required? There's two, so if I click on that 2, this window would pop up and it

would tell me that Illinois and Missouri are the two states that are universally screening for MPS 1.

You can do that for any of your disorders if you want to look at who's screening, considering it, all those different categories in the repository, you can look and identify who's screening. It's a useful tip for states because then we can say, I'm considering adding MPS 1. I'm going to go talk to Illinois and Missouri so I can find out more about their screening status in their state. How they're doing it? So it's a good way to connect states and for technical assistance.

So decision making and policies. How do they make these decisions in newborn screening systems? They rely on advisory committees, the Board of Health, the Commissioner of Health. They also rely on their legislators to make some of these decisions.

But sometimes it's a complex combination of both. That is as you all know a very -- can be a very murky process sometimes and takes

many, many iterations to get through.

So which states have advisory committees? Here we have a map that depicts the number of states who have advisory committees. Those blue states have advisory committees that are mandated by statute or law. So it's in the law that they have to have an advisory committee.

The green states have a voluntary committee. A few states don't have committees now. And this is one piece of a question we got recently from someone from Montana, is okay, who makes up, what states have committees? Who makes up that committee?

So we can tell you, here's the composition of advisory committees. Again, this is compiled across many different states. So this is not any one particular state. But these are the types of people who tend to sit on advisory committees, consumers, lab reps from pathology and chemistry, so this is not the -- public health labs, they have clinicians, hospital associations, March of Dimes representative, ethicists, and then the

newborn screening program.

Again, not exhaustive, but this is a list of the types of people who advise state public health departments on their newborn screening program.

All right, yes, Natasha. And Natasha needs a microphone.

MS. BONHOMME: Okay, great. Natasha Bonhomme, Genetic Alliance. For the advisory committees do you collect any data on how often those committees meet?

DR. SONTAG: I think we do collect that. I'm seeing nods from the back of the row. Yes, we do collect that information. And we also have a place for states to enter the links to the minutes of those websites, that they'd like to enter, where those -- or the minutes of those meetings.

Yes, Deiter.

MEMBER MATERN: Dieter Matern, this is really great but do you verify the information you get back? Because the state that I know well, I'm

sitting on the advisory committee. It indicates that they meet quarterly, but they only meet twice a year. So there's several things that I at least for my state are not the way I understand it to actually be as it is written in your report.

DR. SONTAG: Yes, that's fabulous information. And so, especially that type of information, we rely on the states to report to us. So we sent that back to the states. We haven't gone through our verification process of that level.

Some of the other things we do verify as far as what states report and they're screening for. We haven't got to that level of verification. We did that report back out to the state representatives, but really rely on the community to help us refine this.

So we'd also entertain ideas -- if you have some -- of how we can best go about verifying some of that data, especially as it relates to those types of policies.

MEMBER URV: So Marci, this is Tiina Urv. Are these just external advisory boards, or

you cited, I think New York has internal advisory boards, don't they?

DR. SONTAG: This is as we -- I'm told this is a newborn screening advisory committee. So --

MEMBER URV: Whether it's internal or external?

DR. SONTAG: Internal or external, they're making that decision. I didn't know about internal versus external advisory committees before this, so -- I'd like, I guess, some more information. Maybe after the session, that we can talk about what the -- how the states might differ and shade that?

Okay, so I'd like to talk, switch now to really this orange section. And this is the analytic to post-analytic. We don't have a lot of details breaking up all the different components of this at this point. So I'm really going to circle this entire component and talk about it as a group.

So now this is getting back to those

same 900 infants I talked about a little earlier. About when are they being diagnosed? And so we're looking forward to the day when we have all 4 million babies are in here, and we have 12,000 babies per year being diagnosed with disorders.

So this is a snapshot of the types of data we'll be able to represent to you. But when we think about timeliness, how can we represent this? Now this isn't on population basis; this isn't on all the babies in a state. This is the babies who are identified with a disorder.

So we have here that stair-step of birth to receipt by lab. Happens in the very few first days. And on the Y axis here, we have zero to 360 days, so that first year of life.

So birth to receipt by lab, then birth to reporting out of complete results, birth to that intervention, and then birth to diagnosis. And note that intervention very frequently happens before the time of diagnosis. While you're waiting to confirm that final diagnosis, you're intervening on that child and changing their diets,

doing something to happen, something for that baby to improve their health.

So you look at this and say, I can't really see what birth to receipt by lab is; that's far too squished together. So I pulled these out so you can see: what does this really look like?

Birth to receipt by lab here you'll see that median is about four days of life. So this is data is collected, or the sample is collected, and then transported to the lab. I see a couple faces, people saying, boy, we'd like that to be earlier. That's ideally, sure we'd like it to be earlier, but that's pretty good. Median is four days. And that's just before the time that these recommendations came out, right?

So now we're all thinking about this. We just -- all the states who have courier services just really in place. This is a place that we want to be able to move the bar a little bit.

Now the time to release the out of range results. The median is at seven days. That's what we were hoping for out of range results, right,

from this Committee? Now in here you'll note this is critical and non-critical -- time critical and non-critical results are all put together here. I'm going to pull those apart here in just a minute for you.

And then time to intervention, wide range of time to intervention. Again, it's hard to understand time to intervention when you put all of the disorders together. So we think of being able to pull them apart.

Is that a question?

MEMBER SCOTT: Actually, that was going to be my question for this one and the next one. Can you pull it out by disorder?

DR. SONTAG: Yes, and I'd be happy. Let me pull that out for you. I planted Joan in the audience to ask that question, so I could -- time to confirm diagnosis. Again, wide range of things that we are seeing in newborn screening, and the complexities of that diagnosis vary.

So here's time to receipt by lab by disorder. I'm going to skip through this just in

the interest of time because we don't actually deliver them in a lab by any disorders.

So time to release out of range results by disorder. Now this is important. So you see that CF here, the time to out of range results is -- median is actually less than 10 days of age, which I think is remarkable. When you're thinking of CF tests that also includes for all of the states that are reporting here, they're all IRT/DNA states.

These were -- the states that are represented here are all one screen states. But if they had a positive IRT, they go on to DNA so they're doing both of those. And median calling it out by about nine days of life. Again, there are some that are being called out much, much later.

But then we look at -- whoops, all right -- look at MCAD and those results are being called out at four days. The median is four days. Some are higher, but 95 percent of the babies are being called out before that ten day mark.

Again, gives us room to improve though,

right? We've said on this Committee time critical results, they need to be out by five days. We need to be out there, but we're close. So we can see that we're already thinking of critical and time critical results. States are reporting them out as such, but we have room to improve in that, room to move that needle.

So then time to intervention. Time to intervention for MCAD. Now I want you to note here, the scale here is zero to 50 days. We spread this out so you could really see the data. The scale here is now zero to 200 days; it's a different scale.

So you see the time to intervention for MCAD is almost always happening very early in life. However, there are some cases in which it's stretching out a little bit further. So what's happening there? Those results are getting out to someone. And what's happening with that intervention?

Is it that intervention is not getting reported back to the newborn screening program, and

they're not -- aren't entering it in here? Is it that the intervention truly hasn't happened? And that -- this is a repository. So we're -- this is where we can go back to those states and find out a little bit more information.

But you see a time to intervention for CF is a little bit higher than the hemoglobinopathies who are reported out at about two months of age for the time to intervention.

Now we are not clinicians at NewSTEPs, and so this is where we rely on our clinicians partners to help us think through some of these data and say: where are some of these problems? And I'm looking through the room and seeing many of you in the room whom we've relied on. And thank you for that. As we call you and say, now where do we need to be concerned with this? And going back to those experts who helped us with some of the case definition.

And then time to confirm diagnosis. You can see there is a wide range in time to confirm diagnosis. There's some data challenges that we

have right now with the time to confirm diagnosis with the hemoglobinopathies.

I don't have the time to go into the detail here, but it's actually giving us the opportunity to go back to a couple of states and think about how they're defining that time to -- what does it really mean to have a diagnosis? And how are they confirming that diagnosis? So we're doing it consistently across all states.

So I'm going to go into a little bit of detail specifically for cystic fibrosis. We have quite a bit of data for cystic fibrosis; I'm just presenting five states here.

Again, these are all one screen states, doing an IRT and DNA. The time to receipt by lab, one state's getting their samples very quickly. This is time from birth. So their median here is, I think, two days of life.

Four-five days of life, this state's out to seven days of life is the median time to receipt by lab. Again, gives us an opportunity for moving that needle. Time to release of out of

range results, I'll let you absorb that a little bit.

So you can see, even with an IRT/DNA model, one state is getting those results out -- as reported here -- by about six days of life, six to seven. That's fabulous, but all these states are getting them out within a reasonable amount of time for CF, knowing this is not one of our time critical disorders.

Time to intervention for each of those states. And for CF what does that intervention mean? That's probably they're being seen by a pulmonologist and perhaps pancreatic enzymes are being started. You can see the range, that some of these babies are far out.

And that here, the scale has again changed. With those in the back, the scale goes up to 700 now. So this is almost two years, time to confirm diagnosis. Now you notice on the previous slide, this is -- the scale goes up to 120. Intervention is happening for all these children,

but that confirmed diagnosis is a ways out.

So is it that they had a -- probably not sufficient sweat test? We don't know what's happening here. We don't know the details behind the scenes on this figure. But we can say that confirmed diagnosis tends to happen for CF in the first couple of months of life.

I have data for congenital hypothyroidism here; I'm actually not going to show them. It shows similar trends. We can go into all of those details, anybody wants to have an exciting bear-with-me after the session this afternoon, we can talk about congenital hypothyroidism. We have lots of data like this. We've only been pulling out lots of data. But I just want to make sure I have time to get to the other topics as well.

So, speaking of those data, that's how we are thinking about them from actual cases. But we're kind of taking that and applying it to what we already have as quality indicators. Those timeliness factors are quality indicator concepts

that we have. So I want to talk a little bit about the quality indicators.

These quality indicators have been in development in partnership with the newborn screening community. Many of you in the room were in the initial Committee meetings that we had to develop some of these quality indicators.

The group of eight indicators really spans the course of newborn screening. And the collection of the blood spot out to the reported results and even identifying those false negative, or infants that weren't identified by newborn screening.

So we have them, we've developed them into our repository, we have said okay, now let's start collecting them. And when you start talking to people about how they collect quality indicators, each state has their own different resources for how they might collect those indicators.

And the state says, I'm going to pull

the data, and this is how I think this should be. And the state says, well I'm going to pull it from here. And so the data aren't quite comparable. And it takes a lot of time for them. So we said, we really want these data to be comparable from state-to-state. How can we help them to get there?

So we're starting out with partnering with the LIMS vendors --- the Laboratory Information Management System vendors -- in an effort to assure the data are consistent. So from an idealistic standpoint, we said, all right. You can pull the data from the LIM system, isn't that great? Let's pull it out so it's consistent from state to state.

So you have the same LIMS vendor. You're both using PerkinElmer or you're both using Natus in your same two different states. Can we pull that data out consistently? Idealistically that sounds easy, it sounds fabulous, and as any of you who have ever worked with electronic data management, you know that's not the way it's ever

worked.

As we count up those differences in local collection, I'm going to show you what that looks like. So we had hoped to have really fabulous quality indicator data to present to you today. To say here's what it is across 25 different states. Here's what we can show you. And yet we don't want to show you data that's not really high quality consistent data.

So we are making sure that data is really high quality before we present to you. So the data collection here is deliberate, but it really will result in the high quality data.

So I said we partnered with the vendors. The two that we partnered with to start with are PerkinElmer and Natus, just as we talked about. They are the ones who cover most of the states. Getting them, we have over half of the states.

This is by no means exhaustive, however. Many states have locally developed systems. And many states have other commercially

available systems. So once we have tackled this with these two larger vendors, we are then going to take that next step and work with other vendors and with the local states who have locally developed systems.

I'm just going to give you one example of a challenge we've uncovered in data collection: the percent of invalid dried blood spot specimen cards due to improper collection. This doesn't seem like a hard question to answer. I'm like, how many of you have problems with this, you couldn't test because of improper collection?

And at first glance, we sat down with PerkinElmer, I actually sat down with the state of Colorado and PerkinElmer, sat in a room, and went through each one of these. And PerkinElmer says, well we have this field. But then we talked to Dan White in Colorado, and he said, well yes. But we have additional fields in there.

So under this field that PerkinElmer had developed, Colorado had adapted that for their

own personal needs. So they've said there is other reasons, and these are the reasons they then sent back to hospitals for their report cards. Here's these other long list of reasons as to why a sample might be unsatisfactory.

I'll let you look at them here. But Colorado has done that in one way. And another state has done it in another way. And so now PerkinElmer is sitting down with each one of these states and saying what does this apply to?

If it was contaminated, is that improper collection, or is that improper transport? How do you want us to map these to get them to the right place? So this is a very careful process, and I can't thank the folks at PerkinElmer and Natus enough for really helping us think through this and go through this in a systematic way.

Because this is complicated, and it's very time consuming. And we're all doing this in order to improve the system. But this has taken

some time. It's not as simple as, let's extract data from the electronic system.

So our next steps we are working with them and we're hoping that within the next two months we'll be able to have that data extracted as it is available within those systems. That's with Natus and PerkinElmer, and then for the other states, as I said, we're going to reach out to those and extend our lessons learned in those states.

Okay, so now we've gotten almost to the end of this. Now we've gotten to: how do we evaluate that newborn and make sure that diagnosis is confirmed? And this gets to the case definition project. And we've talked to this Committee before about the case definitions.

It's something that Sara Copeland kind of spurred on us several years ago. And many of the people in the room have been clinical experts working on these case definitions.

We collect this data within our NewSTEPs data repository in order to be able to

provide an accurate characterization of the frequency of these newborn screening disorders. How often are we identifying babies with these disorders within our systems?

So we need systematic definitions both at the local and the national level. As an epidemiologist working at the national level, I definitely want to make sure we're comparing the same thing.

But I'm going to show you an example in a minute of why I think this is so important at the local level, and really from hospital to hospital, and physician to physician, we want to make sure we're being very consistent in how we count these newborns.

So here's this example. Baby with cystic fibrosis, an abnormal newborn screen, elevated IRT, had an F508, and an R117H with a 7T/9T polymorphism. Those of you not familiar with CF, just know that some people who have this genetic makeup are going to have cystic fibrosis.

Probably a milder form. They might be more likely to be pancreatic-sufficient.

Some people with this mutation, these mutations, genetic makeup, might not ever develop any disorders, any disease. So we don't really know what to -- this is kind of a problem -- we don't know what to do with these infants to follow them.

So then we get referred to the CF center. And a sweat test shows results of 25 where a diagnostic is greater than 60. So how do we deal with this baby? So we send the baby on to a clinician. Dr. Smith sees the baby and says yes, this baby has CF.

Follow the baby, and repeat sweat test monthly. Let's in a month, but let's make sure. We're going to follow up these, repeat the sweat test, but we're going to tell the family he has CF. I just have the feeling this baby really has CF. This is my opinion.

Dr. Jones says this baby has CRMS -- cystic fibrosis related metabolic syndrome. And

this is a challenging diagnosis but one that was really created over the past decade to help us identify these babies --- identify and categorize them appropriately so we can then follow them.

So we don't think this is CF, but it might develop into CF. So we should follow the baby every six months and see what happens. Another physician might see this baby. Dr. Garcia sees the baby, and says, you know what? The baby's fine. R117H and 7T/9T, this baby's fine, and it doesn't have CF, doesn't have CRMS, send them on their way. No reason to be here.

Now I know this can happen because I've seen it happen. I've talked to CF clinicians and it absolutely happens. We are not trying to change clinical diagnosis; the clinicians are going to treat them as they see most appropriate. But from public health surveillance, we need to be able to count them.

So how we counted this baby is going to depend on whether they saw Dr. Smith, Dr. Jones,

or Dr. Garcia. And that's not a very good feeling for public health surveillance, right? We want to be able to count the babies -- who did we identify by newborn screening, and what happened to them?

So this is why we have surveillance case definitions, so we can add -- categorize these babies. Our case definitions as they are in place now -- established by a group of experts in CF -- say this baby would be diagnosed as with CRMS using those case definitions.

And we'll tell you now that the burden of CRMS in our country is not well understood. We're all dealing with it on a state-by-state basis. Not well understood, and we think that being able to collect these data and the NewSTEPs data repository will give us the first chance to really understand the burden of this issue with CRMS.

This is just one example. One disorder that goes across all of the disorders that we're screening for. It's critical that we are

collecting them and counting them in a systematic way.

Here's just to emphasize this point, looking through our data repository what we have on CF. Not going to go into too much detail here, but here's two cases with CF. Both have elevated IRTs, both have two mutations known to be disease causing, both have sweat tests. One of them was in the intermediate range of 30 to 59. Babies look pretty similar on paper. One was entered by the state saying, this baby has CRMS. One was entered as CF. That's very likely what the clinicians call these babies. We can now tie those case definitions to these babies, and so we can we count them in a systematic way.

So what are the challenges of our case definitions? It's a lot of work. This is a culture change. We need to be able to collect this information. Some states are already collecting all this information on the diagnostic information in their newborn screening data systems and their

labs, and follow-up systems. Many are not. So it's a time commitment to be able to collect this. But I think it's important, not only from the national perspective, but it's also important at the local perspective.

Yes, Beth?

DR. TARINI: Beth Tarini, AAP. You bring up an excellent point, Marci. And CRMS is obviously something that came. We didn't know until we screened a potentially -- the burden of its existence. Do you think that it would be helpful for candidate disorders to start identifying these case definitions in advance?

So that when they are reviewed by the Committee, there's this sense of at least trying to create these buckets when they're potentially hinted at in advance. Not the case in CRMS. Rather than you working backwards now, trying to define them after the fact?

DR. SONTAG: Beautiful question, and I almost feel like you were planted in the audience

to ask that question. Because the right column here -- the new disorders on the RUSP -- this is one of our challenges. There was a ton of work put into these case definitions initially to develop them. And now we have these new disorders that -- how do we add them?

So I would love to sit down with the review group that's reviewing all of these conditions and say, what information can we garner from that as it leads to CRMS, but also as it relates to just the general diagnosis of a disorder?

There's these unusual cases, but also how do you confirm a diagnosis of PKU, and what are those components? How do you confirm that diagnosis of Pompe? What are the components that are necessary?

So we are really stuck now trying to figure out how do we add those new disorders? It is time consuming, and working off of the -- building from the group here I think would be excellent.

We also have a Case Definition Implementation Work Group, who is helping us thinking about this marketing and communication of these case definitions. And there's a manuscript in preparation that should be coming, hopefully submitted shortly to be published to really summarize this overall work.

So what are our efforts to improve timeliness in newborn screening? Very briefly going to go through this; it's not the focus of the talk, but I wanted to throw this in.

We have been participating in a CoIIN -- collaborative improvement and innovation network. It appears that we have some supplementary funds to work on this. Yvonne Kellar-Guenther has been leading this for NewSTEPs. We have eight states participating in this CoIIN; they're listed here. This is a 15 month project, not funded for the states.

The states volunteered to come in and work on timeliness, improving timeliness. They

are dedicating a ton of time to this. They are doing a great job on exactly zero dollars that we're giving them to do this. And comprised of five individuals from the states. We did have one in-person meeting of them really looking at timeliness to getting that sample to the lab in a timely manner. They have made great changes, and they're coming together to share ideas and find solutions.

Building from that and the success of our CoIIN, we're excited to announce this coming September 1st, we'll have a new funding opportunity, which is NewSTEPs 360. And this option we will support 20 states, and this time we have some money to support states to attack this timeliness challenge.

And we're going to be looking at that over the next three years. This is a competitive funding opportunity that will be announced in the next couple of weeks.

And now we have our PIGs. And I

actually would like to credit Stanford Rich for helping us conceptualize this idea. This is Project Instant Gratification, or PIGs. And this is: what's that hook?

So you are entering data into the NewSTEPs data repository. What does the state get out of it? It's a lot of work to put something in to collect that data. What does the state get out that can give them something to use in their daily jobs?

So we have three categories here. We have the Did You Know Emails, and the Run Charts. And I'm going to show you examples of those in just a minute. And then we also have Personalized Quality Indicator Reports.

And these are things that we'll send to states once we have all those quality indicators in, showing hey, where do you fall compared to other states? So they can see here's an area that I have for growth. And here's an area that I have for, I'm really strong, and I can show this off to my

leadership in my state.

Hopefully you are all on our NewSTEPs LISTSERV and have received some of these Did You Know emails. These emails are just things that we have learned from our repository that we want to share with the community. So this is one that -- Did You Know that we have some queries now that you can go in and query lots of different things. Those queries that I talked about earlier. But look for those Did You Know emails. There's fun facts, we try to highlight states when they do something that's exciting.

And here's a run chart. And I talked earlier about Tennessee and the changes they made by adding a courier service. You can see here that they joined the CoIIN in January and February of this year. This is about the time that they were implementing the changes in their couriers, February-March.

And you see not so much change here, so as we move these bars across, this green bar is

receipt by lab in one day. And this yellow is two days. You see here there were very few at the baseline. It was only less than 40 percent that were being received by two days.

And as we move out, as they rolled this out into more of our programs, they had up here by July and six months in, they had 80 percent of their samples being received early. This is great. This is great for Tennessee, and this is the total that we've given to Tennessee to help them to track and given to our CoIIN participants.

As a part of NewSTEPs 360, we're going to build these types of things into our website so it'll be available for everyone.

So we couldn't do this -- all these activities in NewSTEPs -- without all of you. And I want to thank so many of you in the room. Our steering committee, our work groups, the newborn screening programs who have jumped into this with us and really participating with us.

Our, Jeff Botkin and Jelili, I -- this

was a steering committee meeting? We did get work done, but they, we had a good time, too. So we're moving along, yes -- yes, Dr. Botkin, we're moving along.

The regional collaboratives, thank you for all in the room for the regional collaboratives, our federal partners, our private partners, and vendors. This is a group effort, and I really -- we're so excited to be a part of his newborn screening community.

So we're partnering with newborn screening programs to develop solutions to strengthen the newborn screening system. We have a strong system. How can we continue to grow it and make it stronger?

We do this through quality of data, technical assistance, and by bringing people together to share ideas and activities. And that's one of the key things that I think we can do as the experts in newborn screening and the experts who do the newborn screening. Let's bring

them together. Let's have those conversations, virtually, in person, however we can have them to help improve our systems.

And I can't thank enough, are my NewSTEPs team. I get to work with the best team on the planet. Here's a picture of us responding to Baby's First Test Request for Newborn Screening Month. So it says, "Newborn screening matters because it brings people together to make a difference." It brings passionate people together, passionate people together, to make a difference in the lives of everyday people.

So thank you very much and I'd be happy to take any questions.

(Applause)

CHAIRPERSON BOCCHINI: Marci, thank you for a great presentation. And really it's remarkable, everything that's been accomplished so far. So thank you very much.

Let's open this for questions first from the Committee Members, and please identify

yourself again for the reporter.

No additional questions from the -- oh, Jeff.

MEMBER BOTKIN: Jeff Botkin. This is such important work. Congratulations, and that's the main thrust of my comment. I have a quibble, and it has to do with some of the earlier slides where you referred to the notion of implied consent.

You know, as you know, the whole consent issue has been controversial for decades in this domain. I've not heard this, how newborn screening is approached in most states as implied consent. To me, implied consent means everybody has a mutual understanding of what's going to happen, and there's tacit agreement that that's okay. I think in this context, we know pretty conclusively that most parents have very little idea about newborn screening, and so to me the notion of implied consent is probably not the best term to characterize how these programs are being

organized.

DR. SONTAG: Yes; point well taken. And we should work on the wording there.

MS. BONHOMME: Thank you. It was a great presentation, and I appreciate all the colors and having it being very engaging.

One question that I have is -- so, I know when you present the data and you talk about state one, state two, being able to just compare where states are, but not necessarily -- at least in a public setting like this -- identifying you know who state one and who state two are.

Is that kind of state-specific information, information that you give out to any other group besides that specific state, whether that's at a federal level or if someone was looking at specific information?

And I ask that not so much from a like watchdog perspective, but I think some of this data could be really interesting for people who are on the ground but outside of the state departments,

who want to advocate for newborn screening and want to be able to learn what can they do to really be able to help bolster those programs.

And so I'm just wondering like how does that information get to the people who are outside that state department infrastructure?

DR. SONTAG: Yes, so right now we're still at the beginning stages of knowing, developing those policies. We have a policy that we are putting together a data review group, and requests for data would go through that data review group.

So we are looking for members of that group. We have the general population here to compile that group and say what are those policies, and how can we give data to individuals, because we think it is important for other people to have access to these data in a way that makes sense.

So we're not -- we're respecting the states, and the memo of understanding that we have with the states and data use in an appropriate way.

We're working on that and don't have the final answer yet, but we will shortly.

MS. BONHOMME: And for that group, do you have an ideal in terms of what the makeup of that group would be? And I want to say this is Natasha Bonhomme from Genetic Alliance; sorry.

DR. SONTAG: So we do have an idea of what that group might look like. We would like some people who have some IRB experience. We'd like to have some people who have some advocacy and experience, and some parents on that group. And then some people from state newborn screening programs. So we'd like to have kind of a broad perspective of people to help us --- help advise us.

(Off the record comments)

DR. GREENE: Thank you, Carol Greene, SIMD. Very interesting on those outliers for the diagnosis and the intervention. And you already said but I'd like to reinforce, that there's going to be a lot more information needed before we can

conclude that that's really a problem.

Because the intervention for a child with cystic fibrosis -- you mentioned a good example -- is starting pancreatic enzymes, but not everybody needs them. For some kids with CF, there are people who might say, well I haven't done any intervention. I've simply given them the diagnosis, and I'm monitoring.

But I also want to go all the way back to the retention of data. And the groups that retain data, I think you said for two years or less. And there might have even been a smaller -- a shorter time of retention of data. And CLIA requires the test results be retained for at least two years after the test is reported.

DR. SONTAG: I think there were two buckets there, and the one bucket for data retention -- that was actually the lowest time -- was two years. So I think that was reflected there, how long they keep the samples might have been shorter, but the --

DR. GREENE: Right, and I think you said two years or less for the data retention. And that may need --

DR. SONTAG: And I may have mis-spoke.

DR. GREENE: -- for somebody to go look at it?

DR. SONTAG: Yes.

DR. GREENE: Because less than two years means you lose your -- you fail your recert.

DR. SONTAG: I can't remember where these slides were now, but I -- we'll look into that.

DR. GREENE: I'm trying to channel Ming Chen.

DR. SONTAG: Okay; yes, it does say two, so your -- that's a good point well taken.

Don't know if I can call on people or if -- I don't have a -- go ahead.

MEMBER URV: This is Tiina Urv. Marci, you guys collect so much information. And it was really well, well-presented. But one of the

things I noticed, and one of the things that I've been confused about in the past, is that you just refer to everything as data.

And it would be great, so when Carol was saying the data we collect, or the data that's saved, it would be great -- for people who aren't as immersed in the system -- to know which data you're referring to. So the data regarding -- you know results.

DR. SONTAG: Yes, abnormal results.

MEMBER URV: Yes.

DR. SONTAG: Yes.

MEMBER URV: So, if you just -- I think that would help a lot of outside people realize the breadth of the information you're collecting.

DR. SONTAG: Yes. Thank you.

MEMBER LOREY: Fred Lorey; excellent presentation. I'm kind of like Natasha; I like colors. Could you go back to the slide that showed the ranges of specimen collection times?

DR. SONTAG: I can try; I don't know

where I am.

MEMBER LOREY: And if not, don't worry about it. But it went by pretty fast --

DR. SONTAG: Here it is.

MEMBER LOREY: -- so I couldn't really tell.

DR. SONTAG: This the one you wanted to see, or the --

MEMBER LOREY: Yes, I mean does that -- maybe it's state number three. I often find that it doesn't -- these types of slides don't reflect the California 12-hour collection time. Is that in there somewhere?

DR. SONTAG: California's not in here.

MEMBER LOREY: Okay; that explains it.

DR. SONTAG: Yes, and so this is just a snapshot of eight states.

MEMBER LOREY: Got it.

DR. SONTAG: So your favorite -- this is --- and these are very small samples. These are -- by the time you divide eight states, this is

small. So this is snapshot of what we're going to be able to show on a much larger scale in the future.

DR. CHEN: Freddie Chen, American Academy of Family Physicians. One of the things I enjoy most about the Committee and these meetings is the different perspectives of the different stakeholders, and I want to build on Dr. Greene's comments about case definition and clinical case definition.

And remind us that the needs for surveillance case definition at the public health level are quite different than the clinical management needs for case definition.

And we need to be careful about not implying that one has implications, sort of consequences not necessarily for the other. Meaning that those three physicians may be managing those babies exactly appropriately --

DR. SONTAG: Absolutely.

DR. CHEN: -- even though, in their minds, they've got three different sort of working

clinical diagnoses. And the needs for public health and for surveillance and case definition are a very different sort of level of discussion. So if the implication is for condition nomination and how we approach and discuss those, we have to keep all of those perspectives in mind.

DR. SONTAG: Yes; excellent point.

CHAIRPERSON BOCCHINI: Okay, microphone -- Anne.

DR. COMEAU: Anne Comeau from the New England Newborn Screening Program. Very nice presentation; I have two short comments. One is that I cannot support Jeff's comment strongly enough; implied consent is just not -- that's a foreign thought to me.

Secondly, is being from a regional program -- and I think that what you've done so far is wonderful -- but being from a regional program, I noticed that it looks like many of your responses are state-specific, that don't necessarily fall through into what happens regionally.

So for instance I noticed, I think that New Hampshire said that they weren't -- didn't have reporting 24/7. But we cover New Hampshire and all of our clients so that there is actually the 24/7 reporting. And I think that that might happen in other regional programs as well.

So how you want to handle that, in the reporting so that it makes sense to people who are evaluating what is happening on the ground versus what is reported state specifically might -- you might need to tweak that a little bit.

DR. SONTAG: Yes, we thought about that of: how do we reach out to both the regional labs and the local states? And right now we've relied on the local states to give us that information. But I think it's an excellent point to think of how we can broaden that circle.

CHAIRPERSON BOCCHINI: If there are no other questions or comments, again Marci, thank you very much. Appreciate the presentation.

(Applause)

CHAIRPERSON BOCCHINI: We're now going to move to public comments. We've had a number of persons who have signed up for public comment. Based on the time allocated -- that we have to allocate, each comment should be limited to two minutes.

The first is Elisha Seeger, who represents the Aidan Jack Seeger Foundation. So if you could come --- you could use this microphone if you'd like. Yes, that could be a little easier.

MS. SEEGER: Good morning. My name is Elisha Seeger, and I am the founder of the Aidan Jack Seeger Foundation. The foundation is in honor of my son Aidan, who lost his battle with ALD in 2012. He was just seven years old.

My hope is that in the last few months the Committee has been able to review all of the evidence that shows why ALD newborn screening is so important. The test, the treatment, the cost analysis all points to the same conclusion. We need ALD newborn screening.

The ALD newborn screening test is accurate, as the New York data proves. There is a viable treatment method once the babies are diagnosed. And 90 percent of those boys will also have adrenal insufficiencies. And most importantly is the fact that early diagnosis is the key to saving lives.

Without early diagnosis through newborn screening, thousands of boys will continue to die an early, horrific death. I know the Committee has spent quite some time reviewing data reports, analysis, et cetera. But I what I don't want you all to forget is that all that paperwork is based on human life.

I want you all to see some of the faces of ALD. So this is Aidan; this is my son, Aidan. A perfect charismatic gift, a little boy who'll never get the chance to finish school, play sports, get married, all because his life was taken away much too soon.

This is Jacob, a beautiful blue eyed boy

who died in his father's arms from a fever due to an adrenal crisis. Jacob was just two years old.

This is Steve, a boy who was diagnosed at the age of six, was too late for treatment, and has spent the last nine years of his life in a hospital bed, with no mobility, blind, deaf, and a feeding tube.

Joshua and Eric, brothers both diagnosed with ALD and both lost their lives due to a late diagnosis.

Jacob, diagnosed in August 2014 at the age of six, too late for treatment. Jacob once was an active junior football player, passed away just nine months later this past May.

All of us have one thing in common and the pictures of the boys that I just showed you -- our lives have been destroyed by ALD, never to be mended again. We live with the pain of not being able to save our children. Now I'll show you three more faces of ALD.

This is Matthew. Matthew was born in

January of 2014 and was one of the first boys to be diagnosed with ALD through newborn screening. Matthew is being monitored. And Matthew's mother, Lindsey, now knows she needs to take precautions before having more children.

This is Gavin and Patrick. Patrick was born in New York state in 2014 and was diagnosed with ALD through newborn screening. Because of his brother, Gavin was tested, and he too tested positive for ALD. Luckily, both are not symptomatic and are being monitored.

So now the question is: which group do you want to belong to? I would imagine that the consensus would be the latter. What do these two families have in common? They have a chance that thousands of other families did not -- their early diagnosis.

The early diagnosis puts them on a path to treatment -- for both adrenal insufficiency and ALD -- before it's too late. I want to end with: all of us deserve the chance to a normal healthy

life. If we have the methodology to accomplish this, don't we have an obligation to put it to use? Don't all of you sitting here want the same chance for your family?

Please don't let ALD keep killing our boys. Add ALD to the recommended uniform screening panel. Thank you for your time.

(Applause)

CHAIRPERSON BOCCHINI: Elisha, thank you. Thank you very much for your comments. Appreciate it.

Next on the telephone we have Spencer Barsh from the Stop ALD Foundation.

Spencer, are you on the phone?

MR. BARSH: Yes. Hi.

CHAIRPERSON BOCCHINI: Hi; go right ahead.

MR. BARSH: Okay. All right. Hi, my name is Spencer Barsh, and I am here on behalf of the Stop ALD Foundation. I came before this Committee when adrenoleukodystrophy was first

nominated to be put on the RUSP.

I was 12 years old at the time, and I am now 15 years old and feel even more passionate about the need for newborn screening for ALD. I appreciate you taking the time to hear me out.

I was born with ALD, but my family was not alerted to this until I was one year old. Fortunately, it was the perfect time for treatment. So I went to the Duke Hospital for a stem cell transplant. I have had the privilege to lead a normal healthy life because of my transplant.

I am a member of my school swim team; I've been practicing mixed marital arts for four years, volunteer with Friendship Circle to help children with disabilities, and completed Honors Bio and Honors Math last year with flying colors.

Why is this such a big deal, you may ask? Because my cousin Oliver had to give his life in order for me to have this opportunity. After many years of misdiagnosis, my cousin Oliver was diagnosed with ALD. But by then, it was too late

to help him since transplants do not work at that stage of the disease.

Unfortunately, Oliver passed away at the age of 12 years old, a few years after he was diagnosed. If newborn screening had been available when Oliver was born, he could have been given a chance at life as I was.

So I am here today to urge you to approve newborn screening for ALD. I am alive and healthy today because Oliver was the ALD screen for our family. But one human being should not have to give their life in order for another to live.

Please make sure that no more families have to suffer the painful losses that we did. All babies born with ALD should be identified at birth so they too can have the opportunity of life. Thank you for your time.

CHAIRPERSON BOCCHINI: Spencer, thank you for your comments. We appreciate them.

(Applause)

MR. BARSH: Thank you.

CHAIRPERSON BOCCHINI: And good luck with your swimming season this year.

Next is Amber Salzman. Amber is from Fight ALD, fighting illness through education.

DR. SALZMAN: Okay; I'm also with the Stop ALD Foundation. So good morning, my name is Dr. Amber Salzman, and I appreciate the opportunity to come before the Committee this morning.

As you just heard my son Spencer, my nephew Oliver's post symptomatic ALD diagnosis alerted our family to undergo genetic testing. It revealed the presence of ALD in Spencer, who was successfully treated, as you heard, with a stem cell transplant.

But it also afforded us the opportunity to take necessary measures to give birth to a very healthy girl. However, Oliver slowly lost his ability -- he lost his life at the age of 12 due to the lack of newborn screening to alert him in time for an intervention.

We're fortunate that we have an ALD

screen that works. We have infrastructure to support families diagnosed. There's treatments available. However, to date, only New York screens their newborns for ALD.

As a consequence of New York newborns' diagnoses, these babies as well as their older siblings have been diagnosed in time for an intervention. And in some cases, relatives with the adult form of the disease -- adrenoleukodystrophy -- are comforted to finally get an accurate diagnosis rather than continue to their diagnostic odyssey.

An additional benefit of the early diagnosis is a reduced cost to the healthcare system. As I've seen the success of the New York program, it just deeply pains me to know that children and families continue to suffer and die unnecessarily because of loved ones not born in New York.

The ALD community is very well connected to ALD academics, members of industry,

and is well positioned to address any concerns relative to widespread implementation of ALD screening. Every month that screening is delayed, another fifteen families are unnecessarily devastated.

I respectfully urge you to rapidly move forward to add ALD to the RUSP. And I offer my support, and that of the broader ALD community, to support and aid implementation nationwide. Thank you very much for your consideration.

(Applause)

CHAIRPERSON BOCCHINI: Thank you, Dr. Salzman.

Next is Janis Sherwood, of the United Leukodystrophy Foundation. Janis?

MS. SHERWOOD: I'm actually with Fight ALD.

CHAIRPERSON BOCCHINI: Okay.

MS. SHERWOOD: Okay.

CHAIRPERSON BOCCHINI: All right, so we're --

MS. SHERWOOD: Well, thank you for having me here today. I'm here in honor of my son, Sawyer Benjamin Sherwood, who passed away six months after diagnosis at the age of eight. Unfortunately, he was diagnosed too late for any intervention whatsoever.

We realized after he passed away when we started doing our family history, that my uncle also passed away of the disease, with an unknown diagnosis of brain disease and debilitating arthritis when he was 55.

That was before my son was even born. So had newborn screening been implemented, or had he been accurately diagnosed, we could have had the tools to save my son.

I worked very diligently alongside of Gina Cousineau with the Be a Hero Become a Donor Foundation, and Patty Chapman with The Myelin Project, to get newborn screening approved and signed into law by our governor in the State of California almost a year ago.

And it pains me that we have been waiting for eleven months now and losing boys all this while because we don't have the means to -- I'm sorry, we have the means but we don't have it added to the RUSP, which was an amendment added to our bill at the last minute.

So I'm here to urge you -- please, let's screen all children. But especially let's get these states that have already got the legislation passed to get them screened immediately.

(Applause)

CHAIRPERSON BOCCHINI: Thank you, Ms. Sherwood. Appreciate your comments.

Next is James Luczak.

MR. LUCZAK: Hi. I am James Martin Luczak, and I recently joined the fight for adrenoleukodystrophy prescreening so nobody else has to experience life -- sorry. I have AMN; that's adult-onset ALD. My symptoms showed -- started showing around age 25. And for the last 20 years, I've been on what's called -- what doctors

refer to as "a diagnostic odyssey." That odyssey was primarily funded by taxpayers.

$100,000 back surgery, multiple treatments, doctors to visit, visits to doctors, and specialists --- all treating symptoms instead of finding a root cause. And treating symptoms can get expensive. Conservatively speaking, it totaled over half a million dollars.

Today, I'm 44. I got my diagnosis at 44. What's important is the way I was diagnosed. Last November, my niece moved to New York in the eighth month of her pregnancy, gave birth to a baby girl, and it was screened and tested positive for ALD.

A few months later, after reviewing the charts -- the symptom charts -- I noticed they mirrored mine, and I was suspicious that I too had ALD. That was confirmed this past June. Had my niece not moved to New York, I'd most likely live the rest of my life on an odyssey.

Thanks to Elisha Seeger, Janis

Sherwood, many others -- Aidan's Law, I now know. So, otherwise, I would have given up. So I owe them a debt of gratitude. My family now knows; my mother is a carrier, sister, we all know that there's a killer among us.

And when you know that, you arm yourself. And in this case that ammunition is knowledge. Thanks.

(Applause)

CHAIRPERSON BOCCHINI: Thank you very much for sharing your personal story. We've really appreciate, and it certainly tells us some of the reasons that we're here, and why we're looking at this condition. Thank you.

Kathleen Kelley.

MS. KELLEY: Hi, I'm Kathleen. I'm grateful for the opportunity to speak to you guys today on behalf of the ALD community, as well as Brian's Hope Foundation.

So I'm here today because my brother Brian has ALD. He was diagnosed when he was six

years old. And this is a picture of Brian on his last birthday as a healthy boy.

So Brian was diagnosed because he had a sled riding accident. He slide into a woodpile and hit his head. And after my mom took him to the pediatrician, they suggested he go and get a CT scan which showed some demyelination, which gave further reason to follow up with an MRI.

This showed that Brian had confirmed this frightening diagnosis of ALD. Because of that injury, we still have Brian today. Brian at the age of 20 -- sorry, not today; this is when he was 20. This is Brian last week at 27, a 20-year bone marrow transplant survivor.

Imagine, if you will, how you might feel if you were only eight years old when your brother, who had been skiing Black Diamond Trails and was a talented young athlete, became confined to a wheelchair.

All of this happened within three months. He could no longer talk and could no

longer see me. If this was traumatic for us, imagine how it would was for Brian, to whom all of the terror and horror was happening and how it continues to.

Brian recently had pneumonia three months ago that was pretty life threatening, which took a very physical toll on him, and of course was very emotionally taxing for him. By the grace of God, Brian was born to my great parents, who have provided him with love and all the care he needs. He goes everywhere with us, including trips to Florida in the winter to get him out of the cold.

Despite the many challenges he faces daily, we're blessed to provide Brian with a quality of life in which he is comfortable and takes pleasure in his family and friends, our love, and the rich experiences we are able to provide.

Brian's stoic bravery, tenacity, and wholehearted existence are what have inspired our family, friends, healthcare providers, and our entire community to embrace our cause -- stopping

the progression of ALD.

I'm also speaking to you as a carrier of ALD. Fortunately and unfortunately, Brian was my screen. Now I will have the benefit of genetic counseling and good medical care in hopes of having healthy children.

Thanks to newborn screening for ALD, when the baby girls who have been identified in New York reach their child bearing years, they will know their situation and will be spared the heartache my mother and our entire family has known.

Newborn screening and early detection are critical to assure early intervention and healthy lives. Newborn screening for ALD is life-saving, and you can put it into place today. I'm hopeful that you have come to the conclusion that this test is worthy of a place on the Recommended Uniform Screening Panel. Thank you for your time and consideration.

(Applause)

CHAIRPERSON BOCCHINI: Thank you Ms. Kelley; we appreciate your comments.

That will conclude the public comment section. We'll now take a short break. We are on schedule, so we'll be back at 10:45 to begin the next section of the meeting. Thank you.

(Whereupon, the above-entitled matter went off the record at 10:29 a.m. and resumed at 10:50 a.m.)

CHAIRPERSON BOCCHINI: All right. We're going to get started with the presentation of the systematic review of evidence for newborn screening for X-linked adrenoleukodystrophy.

Dr. Alex Kemper who is the Condition Review Work Group leader from Duke Clinical Research Institute in the Department of Pediatrics at Duke. He is a health services researcher who focuses on issues related to the delivery of preventive services.

He is a member of the United States Preventive Services Task Force, and serves as the

Chair, as I indicated of the Condition Review Work Group for this Committee.

In addition to these activities, Dr. Kemper serves as the Deputy Editor for the Journal Pediatrics which is the official journal of the American Academy of Pediatrics. So Alex, I'll turn this over to you.

DR. KEMPER: Thank you very much. And let me begin by saying I really do appreciate the public comments that were just delivered, because they help put a lot of what I'm going to talk about over the next hour or so into perspective.

And one of the key things to recognize, even before I begin diving into the evidence, that adrenoleukodystrophy is really a complex condition. It has a broad phenotype that can potentially begin in childhood and really go through adulthood in terms of when it presents and the kinds of problems that manifest itself.

So it's a very complex condition. And you'll see as I go through, how we conceptualized

this and thought about it with a goal towards understanding what newborn screening for adrenoleukodystrophy really means in terms of what is it that's being targeted? And what are the potential benefits of pre-symptomatic diagnosis? And what are the potential harms also associated with newborn screening?

And so because it's very difficult and because it's a rare condition, and as you all might imagine there are many, many, many individual case reports, summarizing the evidence can be complex. So periodically I'm going to stop with the presentation and recap where we are and the kind of decisions that we made as a group about how to move forward.

This evidence review also differs in at least one respect than previous ones that we've done in that we had to obtain primary data to fill in specific evidence gaps. This is the first time that we've done that and I'm going to highlight where that came into play, and the strengths and

weaknesses of those data, and how you could potentially consider that as you weigh the vote later today.

So before I move forward this is a list of our Condition Review Work Group. Many of whom have been with us on many other evidence review adventures. I would like to specifically highlight that Jennifer Kwon has joined our group, and she has just been really invaluable in terms of understanding the neurologic issues related with ALD.

And I would be horribly remise if I didn't thank K.K. Lam who's really the engine behind a lot of the work that we do. And then Dr. Fred Lorey and Dr. Don Bailey served as representatives from the Advisory Committee to our group. And helped us when there were key decisions that we were struggling over.

And I believe that Dr. Lorey is now hiding somewhere. We'll be recapping some of the evidence after we're done with this.

So, our goals as usual are three fold. One, is to highlight findings from the systematic evidence review and the supplemental data that I mentioned before.

After I go through that, Dr. Prosser from the University of Michigan is going to be talking about the anticipated bounds that benefit and harm, using data from the systematic evidence review.

And then we'll be capping that off with Mr. Jelili Ojodu from APHL, will be talking about the implementation issues at the state level. We need to take a break I'm told by noon, so we'll have to kind of figure out where things make sense to stop things so that there aren't lingering questions.

I want to make sure that as we go through each section that you have a chance to ask whatever clarifying questions that you might have. And I suspect that there will be many thousands. You know it used to be that I would come up here and

when we presented these things and said well, we'll be able to do this in 40 minutes and end early. And I finally learned that I just shouldn't say that. So there you go.

So we talked before in this group about X-linked adrenoleukodystrophy. And let me just summarize what we've said before. In that it's a peroxisomal disorder that affects the adrenal cortex and the central nervous system.

When I talk about the central nervous system, I'm talking about cerebral demyelination and in some cases spinal cord and peripheral neuropathy.

Understanding the phenotype again, is difficult because there's this progression over time that can happen with affected individuals where they can slowly develop this, problems with their adrenal glands leading eventually to adrenal insufficiency.

And then overlapping with that are the neurologic changes, and eventually the neurologic

manifestations, but not everybody gets everything. And that will make more sense in a slide that I show in a little bit.

Again, it's got a broad phenotype type spectrum. Ranging in symptom presentation that can happen in infancy through adulthood. There are, the males who are affected, the hemizygotes, are nearly all affected with significant multisystem problems with onset. That again can begin in early childhood.

The females heterozygotes -- and you will notice during the course of this talk, and I hope I don't fall into this, call them female carriers, because although it's true that you know that they're heterozygotes, and they technically could be considered a carrier, they do develop symptoms. And I think that just by calling them carriers, we sort of lose some of that nuance.

We didn't focus on the female heterozygotes and what their life course is. And part of that is because you know there's a lack of

data. But from this one study from the Netherlands based on a relatively small number of women, 46 women, that looked at their symptoms in a cross sectional fashion, you can see their ages ranged from 22 through 76 years of age with a mean of 48 years.

And again, these are all women who were seen in a referral center, so they're not necessarily generalizable to all heterozygotes. About 18 percent of them had symptoms before 40 years. And most of them had developed symptoms by 60 years of age.

And there's a wide variety of symptoms that could range from these spinal cord symptoms to myelopathy to peripheral neuropathy, and someone with fecal incontinence as well. So again woman can be affected but we don't have great data on when they do get health problems over their life span, and that, because of lack of data. Again, this is not a focus of our report.

So in terms of the reported prevalence,

overall we're talking about, and I'm going to show more detailed slides about where these numbers came from, but about 1 in 16,900 with males being about 1 in 42,000. And females being about 1 in 20,000. Again, most of these studies are based on finding in referral centers, and then extended family testing.

So when you find an index case, looking and seeing who else in the family is affected. So it's not the same as population level epidemiology. And I would suspect that Dr. Caggana's here and she could come and tell us that once you implement screening for a condition, you find that the distribution of this disorder is you know, different than what you'd expect.

So in the interest of time I'll just highlight the bottom study that used clinical detection and extended family screening, the KKI, the Kennedy Krieger Institute of Maryland did them. The Mayo Clinic in the late '90s estimated that the prevalence of X-ALD in males was about 2.38 per

100,000.

So I talked before about the spectrum of illness associated with adrenoleukodystrophy. And it's interesting. When you go and read the papers, it can be challenging to read because of course cases are described before the biology is completely understood.

And so classifications get developed that may not really affect, may not really reflect the underlying biology. I mean Dr. Sontag was talking earlier about the issues of CF and it is sort of the same thing. It's that all these things are spectrums and when we you know apply a specific disease name to it, it's sort of an artificial construct.

So let's, if you think about the males. A large majority of them, really upwards of 90 percent will develop adrenal insufficiency. The adrenal insufficiency develops slowly over time as I mentioned before. And then later on some but not all males, so I have listed here between 31 and 35

percent of boys in childhood will develop the most severe form of ALD, the childhood cerebral form of ALD.

There's a smaller percentage that can then develop the childhood cerebral form in adolescence and later adulthood. Affected males can develop as adults, can develop a cerebral form, but again that's less common in adulthood but more common is the AMN form which primarily affects spinal cord.

And again, women who are heterozygous for ALD, have this slow progression and it's variable and I can't really comment on it. So again, even though I have things broken into categories, think about these as slow progressions. Or different rates of progression over time, adrenal insufficiency and then the neurologic components.

Let me go through the genetics of ALD and then pause and see if everyone is with me or if there are any specific questions before I go more

deeper. So ALD is caused by mutations of the ABCD1 gene. It's the single causative gene associated with ALD. It encodes for the specific protein adrenoleukodystrophy protein.

The key thing to note here is that the protein facilitates very long-chain fatty acids into peroxisomes. And so if that's not functioning you end up with elevated levels of these very long-chain fatty acids. And that's the basis for detection.

So there are many, many, many, I have more than 600 mutations that have been identified and most of these mutations are unique. Okay. An important thing to recognize is that there is no known genotype-phenotype correlation even within families.

So if you have multiple family members with the same mutation, you can't predict exactly the onset or severity of the disease, which of course makes issues of figuring out treatments and the need to follow individuals carefully over time

very difficult.

So again, I have a lot more to say but I just want to take a pause here to see if anybody has any questions about what I've mentioned before, or if I should continue?

(No audible response)

DR. KEMPER: All right. I'm shocked but I'm going to continue. All right.

So ALD newborn screening is based on measurement of this you know particular compound as a marker for relaunching fatty acids. It can be done in dried blood spots, through tandem mass spec. I'm going to go through more in detail in a second so I don't want to get stuck too much here.

But it can now be multiplexed with Krabbe disease and Pompe disease. Dr. Caggana can confirm I believe that that's being done in New York now. And there's work to be able to multiplex it with the other, with other conditions.

There's a CDC proficiency test, a quality assurance system that's expected to be

available in the fall of 2015. There have been some small technical validation of pilot studies. And because I'm going to focus on the New York data, there's no sense spending a lot of time here. But basically the smaller studies have found low numbers of overall positives.

When you screen for ALD you also pick up other peroxisomal disorders. Zellweger's is one of them. These peroxisomal disorders are not the primary targeted newborn screening. These are devastating conditions for which there's no known specific intervention for the individual at this time. But these conditions are picked up.

Screening with these very long-chain fatty acids, or you know the associated compound up here, which I'm not going to read out because I'll mispronounce it, won't pick up all heterozygous females. It's estimated that between 80 and 90 percent of females will be picked up.

And you know as with all you know

newborn screening, you could you know potentially lower your threshold so that you don't pick up as many heterozygote females but then you would run the risk of missing an affected male.

So it's one of these things we sort of have to balance you know where you're drawing the line. And again, those smaller studies are displaying high throughput feasibility.

So the most important test in terms of confirming that an individual has adrenoleukodystrophy is verifying that their elevations of very long-chain fatty acids in plasma. However you can also go ahead and look for the ABCD1 mutation, but as I mentioned before, because there's no genotype-phenotype correlation it doesn't really tell you exactly what's going to happen to the child in terms of you know being predictive.

New York newborn screening program includes assessing for mutation in the ABCD1 gene. But this isn't really part of the screening, but

it's something that they do to help the referral centers. It's sort of a you know, I heard somebody at one point say, you know it's a courtesy for the referral center to have that done for them. But it's really the elevation of the very long-chain fatty acids that enables you to know that there's a problem.

But in terms of moving forward with establishing a clinical diagnosis and treatment, the mainstay for the childhood cerebral form of ALD is neuroimaging. And by that I mean getting an MRI.

And there's a scaling system that's been developed. The guy's name is Loes. So it's the Loes severity scale. But I always call him Lows because that's how I said it the first time. And now I'm kind of stuck saying that.

So I'll probably go back and forth. And it's confusing if I say the Lows score is lower. You know it's, or the Loes score is less. Or you know either way I get confused, so if he's listening

in right now, I know how to pronounce your name and I apologize in advance.

So it's a scale that goes from zero to 34 with the higher number being worse. The Loes scale is always abnormal in neurologically symptomatic boys. There's been some work that shows that at least in the higher levels where clearly boys would be affected, there's a good correlation with other measures of development, in terms of function, development. Things that the child can do.

And there's at least one study where they looked at having different years to assess the inter-rater reliability, and that was high, had a high kappa score.

So in terms of clinical symptoms, you know these can be really protean and hard to, you know, based purely on clinical symptoms. Say oh, you know this child is likely to have ALD if you didn't have this other information. Because it can be signs of inattention and hyperactivity,

signs of dementia, difficulty in understanding spoken language.

Ultimately you'll have progressive disturbance and behavior, coordination in handwriting, vision, and then you know worsening neurologic disturbances beyond that.

For the boys affected with the childhood cerebral form of ALD, adrenal insufficiency co-occurs in about 90 percent of the cases. Again, there are going to be asymptomatic individuals who may have the ABCD1 mutation and elevated long-chain fatty acids, but be asymptomatic and require follow-up over time to decide exactly what the best course of management for that individual is.

I'm going to show a flow diagram a little later. Yes, Colleen.

MEMBER BOYLE: Just a clarification on the Loes severity scale. So does that just measure the brain MRI, the neuroimaging or does it go to other symptoms?

DR. KEMPER: No. It's purely based on demyelination patterns in the MRI. Any other questions before I move on?

(No audible response)

DR. KEMPER: Okay. All right. So let's talk a little bit about treatment strategy. So the primary treatment strategy for the childhood cerebral form of ALD -- let me back up and just say that really for the purpose of our evidence review, we're focusing on the most devastating form of the condition, which is the childhood cerebral form of ALD that affects boys.

I'm thinking about the nature of newborn screening and the idea of identifying children with health problems. And by my focusing on, or our focusing on childhood cerebral ALD, it's not to diminish the impact of AMN in older individuals. But really focusing on our charge in terms of looking at things that are expected to benefit children, during childhood.

So the mainstay treatment for the

childhood cerebral form of adrenoleukodystrophy is stem cell transplantation. For that you either need to have a matched, related donor -- there's some places that will do, will include heterozygotes, but other centers they feel really you should not include a sibling if they are otherwise matched, but a heterozygote for ALD, because of the risk of it, in later life -- or a closely matched cord blood.

The issue with cord blood is it doesn't have to be as matched as a donor related transplants. And I can talk more about that if you want to hear about that.

The idea is that stem cell transplantation can reduce the risk of progression in the neurologic symptoms. If you detect the cerebral form early enough. There is risk, risks associated with transplantation of course, including graft-versus-host disease.

There's both the acute and chronic graft-versus-host disease. And your risks with

developing that really depend on the degree of match, the age that you are at the time of transplantation. So the younger children have a slightly lower risk of developing ALD than, or graft-versus-host disease than older kids. And then the GVHD prophylactic regimen that individuals are put on.

Because of this big variation it's hard to succinctly summarize this, but if you look across transplantation for non-malignant, non-cancerous conditions, the risk of mortality in the first year or two is on the order of five percent, maybe as high as eight percent. Again depending upon the source of the transplant.

And you'll see that in a little bit when I show you some of the outcomes, where there's like a little blip down around the time of the transplantation. There's also this risk of failure to engraft. So for whatever reason the transplant doesn't take. That's my sort of very simplistic sense of things.

I found at least one case of that that was reported and that child was given another, I don't know if they call them units or whatever, another bolus of transplant, magic stuff. And that was effective.

(Laughter)

You know I'm a general pediatrician, so I'm very reductionist on this stuff. So the transplant does not help with the adrenal problems. Okay. So if you, you know, have adrenal insufficiency, you still need to have replacement therapies.

So you know, oral steroid replacement. So again, these are really very different issues. There are a few other treatments that are out there that we're not going to talk about. We're not going to talk about gene therapy for X-linked adrenoleukodystrophy.

There's some case reports out there. There's a company that's very much involved with this. This is really sort of future work and you

know I'm hopeful that it's effective, but really can't comment today on it. So it doesn't really factor in to when we talk about benefits of therapy.

Lorenzo's oil, I think many of you might have heard about that. The oil supplement that was developed for boys with adrenoleukodystrophy. There's been a lot of work that's done, that's been done including a Cochrane review that questions the value of Lorenzo's oil.

And so again for the purpose of the presentation today, we're focusing on transplantation. And then N-acetyl-L-cysteine, which reduces oxidative stress through the glutathione pathway, it regenerates that, can help with advanced brain involvement by reducing oxidative stress.

Again these, from what I can find, it's really only been tried in very severely affected, later stage cases. And for the kinds of things that we're talking about in terms of presymptomatic, identification doesn't really

come into play.

So again, Dr. Botkin.

MEMBER BOTKIN: Sort of two questions. You mentioned that stem cell transplant doesn't influence adrenal cortisol treatment. Are those aspects of the disease entirely independent? In other words does treatment of the cortisol deficiency influence at all the rate of neurocognitive impairment?

DR. KEMPER: No. Years, that's an excellent question. Something that we really, we're trying to tease out. And I, the way I conceptualize this is really, you know although it's the same common pathway in terms of the peroxisomal disorder and there's like it's response that injures both the myelin in the brain and affects the adrenal gland. For all intents and purposes, I think of it as like two trains leaving the station. They're independent but related.

MEMBER BOTKIN: Okay, separate question then. Does adrenal cortisol deficiency

even if treated, complicate the stem cell transplantation? Does it raise the risk of the transplant because that other aspect of the disease needs to be carefully managed?

DR. KEMPER: Yes. I mean it certainly complicates this thing because children who get a transplant are at risk for thing like infection. And if you didn't you know, weren't addressing it, and they developed stress, they could, you know that could lead to death.

But I talked to one person who does a lot of transplants about this very issue. And she said that you know the, if the concern is because the child's on steroids all the time that it lowers their you know immune function. And then you know makes the, you know somehow it complicates the preparatory regiment before the transplant, or the engraftment later. She didn't think it did. And the reason is because it's just really physiologic replacement that they're getting.

So to answer your question, it's

something that clinicians need to be very careful of because of the risk if you didn't replace it. But it doesn't, at least in this expert's opinion, alter the outcomes from the transplant itself. Again, this is expert opinion and I don't have data to answer that.

MEMBER SCOTT: Joan Scott, the Les (sic) or the Lows (sic) scores, is a description on MRI findings about the amount of cerebral involvement. Can you correlate that to a functional status so for an example and eight year old boy with a Loes score of 3 --

(Simultaneous speaking)

MEMBER SCOTT: -- be compared to another eight year old boy with a Loes score of 3 as far as the functional?

DR. KEMPER: Yes, so there is one study that was done that looked at the, and there's probably, there may be other studies, but one type of the study that we included in the review that specifically looked at that question. Where they

looked at the Loes score and they looked at the function of the child.

The thing that was interesting, it's described in the report. I don't have a slide on it, is that the Loes score that they were using was pretty high. Like higher than what we would hope for a transplant. Within the range that they used, there was a linear association between a whole bunch of different measures of development.

But because it started out relatively high, we're going to spend most of the time talking about Loes scores in the zero to five range, you know something like that. And I can't tell you like well, a three means this.

What I can tell you is that in somebody with a Loes score of like nine, or 10, or 11. Is someone who's going to have you know really profound problems with their development and cognition and ability to do things.

But I can't, I don't know if it continues to be linear below a certain point. And

it probably isn't. And you know we can certainly bring in some of the experts later if you want to hear their perspective. But it's only in this higher range that we have those data.

Anything else? Okay, again I'm kind of shocked. All right.

So this is a figure that we've taken from this one publication. It's referenced below as an algorithm for the management of presymptomatic adrenoleukodystrophy.

And so what they posit is that MRI's a sensitive and reliable marker for the disease progression. We're going to talk about this. That the Loes scores severity rating, less than nine is recommended for transplantation. Okay. And then they recommend having an endocrinologist involved with monitoring adrenal function.

So once the diagnosis of X-ALD is made they recommend referring to an endocrinologist to monitor the adrenal function and then to obtain a MRI. If the MRI is abnormal then it goes on to

consider BMT again. I didn't edit this slide for the language that we're using but, that's the same as the hematopoietic stem cell transplant.

If the MRI is normal, and they're between the ages of 3 and 12 then they can, they go through repeat MRI every six months. And if not, repeating MRI every 12 months.

So right now you know, as you all know, New York state is the only state in the union that's doing screening for X-ALD and they're leaving the management to the individual treatment centers.

But from conversations that I've had, this is the general pathway that they were following. Of course you know they may choose to get an MRI more or less often. But I put this slide up here just to give you, you know a flavor of the kind of management that needs to be done with presymptomatic identification. Okay. All right. Move along.

Now we're getting to the evidentiary definition, a time to see how we're doing. Okay,

perfect. So I don't want to bore you with our key words and process but just to know, there are a lot of articles. And thank you to K.K. for keeping this organized and on top of things.

Many of these were really small case series. It's hard to generalize from them. You'll be happy to know that I'm not going to talk about each individual article, but again keep us at the 30,000 foot level. To again, focusing on the lessons that we've learned about the potential benefits and harms of presymptomatic detection. And how well screening works.

So we are very fortunate to have a number of experts who agreed to talk with us on a regular basis. They're listed here. We had three formal TEP meetings where we reviewed things like cases definition, natural history, prevalence, screening diagnosis, treatments and so forth. And also searching for unpublished data.

I do owe a big thank you as well to the technical experts because I did send many emails

in between time for their information. And I didn't put Dr. Salzman's name up here as well, but she was very helpful for hooking me up with some specialists as well. So thank you for doing that.

This somewhat overwhelming slide is the New York newborn screening program, short-term follow up algorithm. And I'm going to go into more detail about the screening and the screening results, but I just want to show at a high level.

And I'm not sure how well you can read that, but at the time that a positive screen is confirmed the gene is evaluated. And if a mutation is found, if they're a boy and they have elevated very long-chain fatty acids, and that confirms the diagnosis of ALD.

Females can either be carriers or have peroxisomal storage disorders which sort of goes on from the right, and you'll see the different categories there. The neat thing though, again there's that big branch point at the top around the ABCD1 mutation. But it's really measuring the

very long-chain fatty acids that helps put individuals into the sort of appropriate buckets that you see on the bottom, which is why you'll see for example X-linked adrenoleukodystrophy is repeated twice, once in both arms.

The other thing associated there, the low plasmalogen. I hope I said that right. It is a marker for the peroxisomal storage disorders. Remember that when you screen for very long-chain fatty acids you pick up these other peroxisomal storage disorders which are not the targeted screening but are you know clearly devastating illnesses.

So let's talk about the New York newborn screening program. So there's a Tier 1, based on Tandem Mass Spec. And if that's abnormal then the test is repeated on the same dried blood spot.

Of the, these data go through the end of July. Of the about 360,000 newborns that were screened, about 1.8 percent of them had a abnormal first tier test. And were, came back for an

independent specimen. And once that was done and then through the process of mutation analysis there were 33 out of the, you know this large group of newborns that was screened.

So in terms of findings they're were 14 boys with the ABCD1 mutation. And the last time I spoke to Dr. Orsini, which was a couple days ago, of those 14, seven were confirmed to have X-linked adrenoleukodystrophy based on having a separate lab measure the very long-chain fatty acids. And he thinks that it's likely that all 14 will be, or perhaps have already been confirmed. It's just that the New York state lab hasn't gotten those reports back.

So the key thing is 14 males with the mutation, who at least on the screens has had elevations of very long-chain fatty acids. Seven of them have been absolutely confirmed, the other seven are still either in the process of being confirmed or have been confirmed but not reported back to the program.

There have been -- oh, see I knew I was going to leave carrier there at some point. So I apologize about that -- 14 female heterozygotes and then there were five other conditions. Four with either Zellweger's or related peroxisomal storage disorders. And then one with a Aicardi-Goutieres syndrome. Probably mispronounced his name as well.

So that's not a targeted screening and from all I can tell people were kind of surprised that that kid got picked up. That is a condition that's associated with encephalopathy. So I don't know, somehow that you know affected the very long-chain fatty acids. But again that was kind of a surprise and not a target of screening.

So as we move along, one of the things that you all as Committee Members are going to have to think about, is what's the target of screening? Are we trying to just identify the newborn males with X-ALD who are likely to go on and develop the most severe form, the cerebral form? Or is it to

identify female heterozygotes? Or is it to identify other individuals who may you know develop very significant symptoms but later in life? Because that does affect how you sort of propagate things.

Working with our representatives from the Advisory Committee, we really did focus on the childhood cerebral form. Part of that again is because these are the kids that are likely to have problems early in childhood, reflecting what the Committee has generally put a focus on for newborn screening. And also because that's where the most data are that would allow you to understand what might happen as a result newborn screening.

So remember I told you I was going to take a break sporadically. I want to summarize where we are. Because again, it's very easy to get lost in this. Okay.

So the overall prevalence of adrenoleukodystrophy in males and females is about six per 100,000. And the prevalence, the expected

prevalence of males with the childhood cerebral form is about one per 100,000. As I mentioned before there's no genotype-phenotype correlation.

Screening is based on detection of elevated very long-chain fatty acids. Screening also identifies most, but not all, heterozygote females. And will also pick up some individuals with other peroxisomal storage disorders.

The New York newborn screening program has a low total rate of positive results. So if you look at the number of individuals that tested positive, it was overall low.

We'd like to also report back the positive predictive value, and of course the positive predictive value depends upon what your goal of detection is. In all of our work, we were focusing on the boys with X-ALD. And if you assume that all 14 of those boys that are in the process, who have already had their very long-chain fatty acids measured, actually do have varied elevations. Then we're looking at a 42 percent

positive predictive value, or 14 out of 33.

And then in summation the diagnostic follow up includes MRIs, an assessment of adrenal function over time to either determine the need for a stem cell transplant or adrenal hormone replacement.

So that's just as far as we've gotten right now in the evidence presentation. Before I move on to the next part. Yes.

MEMBER MCDONOUGH: Steve McDonough, didn't New York detect more cases than they were expecting based on the previous estimated prevalence?

DR. KEMPER: Well, from my take on the whole thing, it fit in into the ballpark of you know how the numbers look like they would play out. One of the things that's challenging for us is they just picked up these cases so it's hard to know if they're going to develop the childhood cerebral form.

So this is a nuance that I hope I can

transmit, but I'm afraid I'm not, which is that when you start screening for things, you pick up a lot of stuff beyond just the most severe cases. You start picking up, you know right now we expect that most boys with ALD will go on to have the childhood cerebral form. But when you start screening, maybe you're picking up more mild cases that might not have come to clinical attention the same way. So it sort of redefines the know epidemiology of the disease.

But if you kind of look at it and assume that most of these boys go on to develop the cerebral form, then it kind of hangs together. But I hate to say that until you know more time passes. Did that make any sense? I'm afraid I didn't -- okay that was, I'm going to go for that.

All right, what other questions? Dr. Botkin.

MEMBER BOTKIN: I wonder if you'd go back a slide? I guess I want to hear your explanation again, or whatever additional

information you might have about the kids with, the boys with ABCD1 mutations, but we don't have any clinical information on. These are kids that have been detected over a fairly long period of time. So these kids are not all newborns at this point. Right? And so --

DR. KEMPER: Well as it turns out --

MEMBER BOTKIN: -- what's the explanation of not having more follow up data on these kids?

DR. KEMPER: Well, so as it turns out, like I think God loves doing things in batches, because there was this little blip that happened later on. I don't know why that is, but so, I spoke at length to Dr. Orsini about this.

And he said you know once they identify the children, they make sure that they get to the treatment center. But they have less control in getting clinical information back from the treatment center. They know that they were there but they just haven't gotten the values back yet.

And I, you know I know Dr. Caggana's in the audience and I don't know if she wants to say anything else about that or make sure that I didn't misstate my understanding.

I knew I was going to call on you too. I was like so happy to see you here.

DR. CAGGANA: Okay, so the reason is we close the case with the diagnosis when we get a form back from our provider, or we get an electronic transmission that they've, you know we know they see the children, they know the appointment's scheduled. But in our system, it's not closed until we get that diagnosis back.

We have some, you know we have some antidotal that they went and the very long-chain fatty acids were elevated, but we don't close that case out in our system until we get that, all that information back from the provider. And sometimes there's a lag in that and we go back to the providers and say any follow up on this baby? So that's one reason.

Of the seven kids that we've seen, they've all had a mutation, they've all been positive in our test. We've gotten the diagnosis back, and the very long-chain fatty acids have all been elevated.

So that's why we're pretty confident that those, all those babies with the mutations are going to be -- and we also have when we first started screening, within the first couple months we had this sort of bolus of referrals. And then we went a fairly long period where we didn't have referrals, which is part and parcel to screening. And then we went back and sort of got another batch of them. So it's kind of an interesting ebb and flow. But we see that with other conditions.

And so there are time lags. It's not like every month you know if you calculated it out based on how many babies we're screening, we see two per month. It doesn't work that way. So there are lags in the feedback we get. That helpful?

DR. KEMPER: Thank you. Dr. Greene.

DR. GREENE: Carol Greene, SIMD. I'm just curious about a statement you made just a little bit ago, that if we assume that most of the boys who are identified by the newborn screening --

DR. KEMPER: Yes.

DR. GREENE: -- have the cerebral form --

DR. KEMPER: I should have said 30 percent.

DR. GREENE: Thank you.

DR. KEMPER: Thank you, that's a very important correction. That was a speaker's trip over what I meant to say.

DR. GREENE: Yes, because that's generation of --

(Simultaneous speaking)

DR. GREENE: -- looking at families.

DR. KEMPER: Yes, but the numbers, right, right and the numbers still kind of make sense. When you do that --

DR. GREENE: We just heard an eloquent

example of --

DR. KEMPER: Right. And you'll see Dr. Prosser, when she presents the modeling based on this evidence, it's actually going to make a lot more sense than me giving sort of qualitative estimated -- Dr. Caggana.

DR. CAGGANA: I just wanted to clarify one other thing. On the table that you see up there, Tier 1 and Tier 2 testing are all done in the lab on the same sample. I know it says it on there, but I think when you said it, you said a different rate.

So what happens is we do the Tier 1 testing which is the mass spec with the Krabbe and Pompe tests. And then internally if it screens positive in that setting, then we go back to that same card, take another punch and we run that Tier 2 --

DR. KEMPER: Right and then it's after that they move, yes, so it's a thumb print.

DR. CAGGANA: So that 1.84 percent is

the rate of retest in our lab, not where we go back out to families and ask for another specimen. So I just want to clarify that.

DR. KEMPER: Dr. Boyle.

MEMBER BOYLE: This is Coleen Boyle. And this is a bit nuance, but within families, thinking about that 30 percent with the cerebral form. Is there any knowledge about whether that, given that the first child would be the presenting with symptoms, with cerebral form. Is it higher within families where there's a family history versus like general population? I know that's probably not --

DR. KEMPER: You mean your risk of having another child with the --

MEMBER BOYLE: No, no, the prevalence of cerebral form of ALD? So is there more of a concentration within a family that already has one child impacted, or is it?

DR. KEMPER: Yes, I can't comment on it other than to say that people talk about how there's

no genotype-phenotype cor -- but you know what happens is you know you got a case here, and a case there. And it's only the large treatment centers that report things. So I'd rather not guess. These are great questions though.

DR. KEMPER: All right. Oh, yes, Dr. Botkin.

MEMBER BOTKIN: If you go back to that slide again. I know our focus of course is on the males for the primary purpose here, but I'm interested in how the state, New York state is managing information about the female heterozygotes. Is that a letter, and is that it? Or is there a medical evaluation or what's happening with those results?

DR. KEMPER: So it's my understanding and Dr. Caggana, you correct me if I'm wrong. But those females are also getting referred to treatment centers. But it's up to the treatment center in terms of the subsequent management that they do including the things like extended family

testing if that happens. Is that? I don't know where you went, Dr. Caggana. You're hiding back there somewhere.

(Off the record comments)

DR. KEMPER: Okay.

MS. VOGEL: Hel Beth Vogel, we'll go on the boring screen. I follow up in New York. All the females are referred to the center and get genetic counseling. They don't have additional testing done. But a full family history and genetic counseling session happens for each one.

DR. KEMPER: Right, and so it's up to the clinician in terms of how they use that information as well then.

MS. VOGEL: Right. Yes, I mean they, you know it's, the important thing is looking at the family and making sure that any potentially affected males are brought to attention.

DR. KEMPER: Dr. Boyle.

MEMBER BOYLE: So before you run away, one more question, Coleen Boyle.

DR. KEMPER: It's never that easy.

MEMBER BOYLE: No, relative to the, I guess the treatment and the clinical care network in New York, I know from the base on the Krabbe experience that you've setup a fairly intricate follow-up system. Is something similarly been developed for ALD?

MS. VOGEL: Yes, so before we started screening, we were fortunate enough to have Dr. Raymond, I don't know if he's here, but Dr. Raymond worked really closely with us and the nine metabolic centers in the state. We developed protocols for minimum sets of testing.

You know there's some centers that may chose to do more but we developed a minimum that are testing for each baby who screens positive. That was part of the very tiny box flowchart that you saw which did not start out with that many boxes. But it developed to that over time.

So we developed that minimum standard evaluation of each child who screens positive for

ALD would have it at one of our nine centers, whether it's a male or female. So that there is some standardization. And a recommendation that came from the group all agreeing as well Dr. Raymond.

DR. KEMPER: Other questions? Dr. Lorey.

MEMBER LOREY: I don't know if anybody has an answer to this, but in light of the fairly high percentage of female carriers that have symptoms. Has there been any discussion of reclassifying the mode of transmission of this disorder?

I mean it wouldn't be considered co-dominant obviously. But it's not acting like recessive either.

DR. KEMPER: That's above my pay rate.

MEMBER LOREY: Maybe you wanted to excel the ex --

(Simultaneous speaking)

DR. KEMPER: That's, yes that's not a, you know but actually what's interesting though is

that really speaks to, you know as we go back and review the historical data. You know some stuff in the 80s and 90s. It's just interesting how people refer to the condition and how the conditions really change. Again I think it speaks to the fact that you know often times when we talk about diagnosis, they're really these constructs we put on top of very complicated things.

So it would make sense to do that. And I think that there is some simplification around the terminology, around the ALD that's going on right now.

All right. So I have a question for you all, which is it's now about 17 minutes to noon. I can start with presymptomatic versus clinical detection outcomes and stop. Or should we break a little bit earlier? I just don't, because it I think kind of hangs together.

(Off the record comments)

DR. KEMPER: Okay, I'll keep going. Okay. And I'll say what I always say, I'm confident

that we can get through the section.

All right. So what are the benefits and harms associated with presymptomatic detection compared to clinical case detection?

So the question that we're charged with is if you identify a newborn with the condition, what do we expect the benefits and harms of that to be?

I don't mean to minimize the fact that ALD is a, you know really terrible condition. We all agree about that. But our job is to really dig in and see what we can learn about the presymptomatic detection. Okay.

So let's talk about adrenal insufficiency first. This is going to be the easy one to get through. So untreated adrenal insufficiency can lead to death. And there's certainly, you know scattered case reports of that kind of thing.

But there is no study and by that I mean, you know something its nominator in the systematic

evidence review. Where we could directly compare treatment outcomes based on the timing of diagnosis of adrenal insufficiency.

You know the adrenal insufficiency is not like you know one morning you wake up and all of a sudden you're adrenals are non-functioning. It happens over time. And so evaluating in the kind of retrospective study, again you know this is prescreening, what the, you know what the potential benefit of identifying adrenal insufficiency is hard to do. And we just couldn't find it.

There's one study that's referred to a lot that was published in 2011 that talks about, if you look at all the people who show up at a referral center with adrenal insufficiency, was there missed opportunity to identify ALD?

Right. So somebody was, you know was treating their adrenal insufficiency but it never occurred to them to test them for adrenoleukodystrophy and certainly that can happen.

But this study didn't address the very narrow question which we're interested in, which is if you identify somebody earlier with adrenoleukodystrophy, what's, compared to late, what do we know as the outcome?

Again, and I, we heard during the public comment period about how missed adrenal insufficiency can be devastating but we weren't able to find the kind of study that we would need to talk about the, you know potential you know risk reduction.

We talked about before how transplantation does not affect adrenal insufficiency. And because of lack of data, for the next part of the talk, presymptomatic detection of adrenal insufficiency isn't the focus of what we're going to be talking about.

Not to minimize the, it happens or doesn't happen, but just the lack of evidence around early detection of adrenal insufficiency.

All right. So now, let's go back to our

buddy Loes and talk about treatment outcomes using the Loes score as the, as both the outcome and the predictor. Okay. And you're going to see a bunch of slides over there.

There are other scores as well. There's a neurologic functioning score and also an ALD disability rating scale. Most of the studies focus on the Loes score. And that's what I'm going to be talking about in the next little bit.

So this is a historical description of the five year survival after symptom development with, and by untreated is untreated with transplantation. And you can see there's this big drop off in survival. Okay.

There's five years after symptom development there's a 66 percent survival. And if you go out as far as ten years, there's a 43 percent survival. There are lots of pictures like this, and I'm going to show you some more grafts like this.

For our purposes these kinds of data are really difficult to interpret because the zero

isn't, you know the zero at the child is born. It's zero after the development of disease symptoms which varies per child.

So this slide tells you that there is this you know, dramatic rise in mortality after the development of disease symptoms. But it doesn't help us understand the age of the child. Okay.

So again, what I'm showing you here has been replicated in other places and I just want to show you. This is five years survival after the first abnormal MRI. Okay. Stratified by the line at the top, is a Loes score, less than nine and a neurologic function score of zero.

And I think a copy of that's in the report, but basically it's the neurologic scale is really based on some fairly gross measures, not gross like gross motor, but you know big categories. Of the children who got transplanted with less neurological involvement, you know you can see the survival at 95 percent. If they had greater involvement, post transplantation, or you know I'm

sorry. I did this actually last time on the MPS one as well.

Let me redo this, because I'm thinking about a future slide I'm about to say. This is transplanted versus not transplanted. Okay. And you can see the transplanted ones, let me redact that from the thing. Because I was thinking about the next slide.

So the individuals who got transplanted, their survival probability was 95 percent if they had less involvement. Okay. The non-transplanted individuals you can see had this dramatic drop off. What I meant to show you, actually it's going to come over here.

Let me just, this is just a slide to show you that there's been a bunch of different studies that have all looked at early versus late stage transplantation. And late stage I mean greater involvement based on the Loes score. Okay.

So this is the slide that I was thinking about showing you, and I got ahead of myself. So

the solid line at the top, okay, shows you outcomes from transplantation for individuals with Loes score, less than nine. Okay. And no other gross neurocognitive deficits.

The dash line where they, where you know there's the bigger fall off, is the Loes score of greater than nine and more deficits. So you can see over on the left-hand side, the table in terms of the median age of the subjects and so forth.

Again, I'm trying to keep this best I can at the 30,000 foot level and you'll understand why in a little bit. But the key thing to note is that if you get transplanted with greater involvement, and greater involvement being in this case a Loes score of nine or above, then your treatment outcomes are worse. All right.

This study suffers the same sort of problem I was talking before in terms of the time the zero is, this is all you know time post transplant. So we're not talking at a standardized age.

This has been shown over and over again. In multiple different small cohorts through really case series studies I should call them. That transplantation with greater cerebral involvement is associated with worse long term survival.

And that's why in that little algorithm that I showed you, there was you know, recommended transplantation for you know Loes score of less involvement.

Dr. Boyle.

MEMBER BOYLE: I just a clarification. Is that the, what I heard you say, was that the treatment actually may impact the survival, but I was just looking at it as saying that the treatment doesn't arrest the disease. Is there a difference? That the treatment doesn't actually --

(Simultaneous speaking)

DR. KEMPER: Well you see that's actually --

MEMBER BOYLE: -- does it actually impact it, because that's what you were saying?

DR. KEMPER: No. What I'm saying is that if you, yes, if you go -- you know I'm going to use, I believe my maps will come up. Okay.

So these are the treated individuals. And what you often times see in the treated individuals, is this little drop off, right here. And that's probably the mortality associated with the transplant itself. And then these guys do okay, right.

It, this slide over here shows you these are the transplanted, these are the non-transplanted kids. So it does seem that and again, this is mortality. This is not measures of neurocognitive involvement, but I can tell you at least if you sort of read in-between the lines in the statement, that it does arrest further cerebral involvement. So you know the Loes score. I know I don't have a slide on this, but you know the Loes score tends to plateau as well.

There have been a couple of the case reports where the Loes score got marginally better,

but it's hard to know what that means functionally. So when you transplant, you know you have this risk of the transplantation. Right here, which is what I think this line is.

And you're going to see this in other things I'm going to show you in little bit. And then they go along with survival. Non-transplanted you can see the risk of death you know continues to go down like that.

So let me be clear again here, that transplantation does reduce the risk of mortality. Okay. But in that you want to have your transplant done at a lower Loes score. Okay. And because of that, most treatment centers won't do transplants after a certain amount of involvement.

Yes.

DR. GREENE: Carol Greene, SIMD. I think I want to restate Coleen's question a little bit and amplify it.

DR. KEMPER: Yes.

DR. GREENE: There are at least two

reasons why somebody with ALD, who had a more involved neurologic problem could show the higher rate of mortality that you're seeing. My personal understanding, it's both. But you're much more steeped in this.

One would be that there is already enough neurologic damage, and that the mortality is related to things like pneumonias that come along with the neurologic.

DR. KEMPER: Exactly right, so where when we --

DR. GREENE: The other is that the neurologic problem, that the neurologic disorder, that the disorder progresses despite the transplant. Because it's already worse. My understanding was that it's both, you may know more.

And I think Coleen's question was, does the neurologic disease progress? And you can't count on the stability there at four, five years out because you see that in the non-transplanted group as well.

So I think the question is, what's the cause of mortality?

MEMBER BOYLE: It was the former then. I just wanted to know whether the treatment in fact was negatively impacting it, not that progression continued. Just our help.

DR. KEMPER: So we have. I'm going to put my sort of evidence hat on as well. Because we have you know interpreting these data can you know they're often times little small studies.

It's hard because the Loes score it both a predictor and an outcome. And we know that they you know change over time. And then it's confounded by the age that they come to attention.

And then there's often all sorts of things that are never reported in terms of you know how the management was done or exactly what the kind of transplant was that they got, it they got a transplant.

And even you know, in many of the studies the final cause of death isn't described. So there

certainly could be things related to you know pneumonia and aspiration for an individual who has profound neurologic deficits. I mean it could be you know really any number of things.

So the way I did this, again I'm going to show you something that will make, I hope make all this make more sense. Is I tried to be agnostic to what the final common pathway was.

And just think about, like well if you found these kids earlier, regardless of what happens to them, does it make a difference because there are just too many variables to think through this.

We tried doing it and couldn't get there. Let me because I think the next, okay. I'm going to do the next two slides if that's okay, Dr. Bocchini and then I think there's a good stopping point. Okay.

So here's another study from a single center that focused on cognitive and gross motor development. They're not very many states like

this that I could find. But this just basically stratifies individuals by their -- this is, the green line here is the normal progression.

The boy, I apologize, it just didn't come out very well, but the individuals with the lower Loes scores are in the blue. And those with the lower Loes scores are either in red or in black. The children represented by the black line didn't survive. Where's those in the red are still around.

It shows developmental age over here. And this one is actually helpful in terms of it having calendar age, not age since the development of symptoms.

And so you know take this as a very small study and you know as Dr. Bailey I'm sure will point out, there are 10 million confounders that we can't adjust for. But it does seem that the individuals in this case is less than you go to ten. We're having better outcomes in terms of development than those with Loes score above ten.

Okay. This is like really, really small numbers and I don't want to over play it, but I think it helps at least give a, put it in perspective. Okay.

So here was the issue for me. Okay, I'm going to like, leave a cliffhanger. Okay, which is the key question that we're charged to look at, is does presymptomatic identification lead to improved outcome, compared to usual case detection? Right.

Because that's the argument for newborn screening. Okay. So we had these case series suggested there are better outcomes after transplantation when the Lows (sic) score is lower. Or the Les (sic) score is less. Depending on how you like to think about it.

But regardless there's, the published studies do hang together. Now different studies dichotomize it different ways. It's nine or ten or eight, but in any case it seems like there are better outcomes regardless of what the mechanism is.

Okay.

The second thing is that the transplantation doesn't lead to restoration we've seen in brain involvement. So if you look at seeing different patterns in demyelination, the transplant itself doesn't cause restoration of that. But stabilizes things. Okay.

But our question was, you know, is there an ideal threshold for transplantation? So we've been looking at these scores of eight, nine, ten where kids are more profoundly affected. But you know what does it mean to get transplanted at you know, .5, 1, 2, that kind of thing.

And then the other challenge that I pointed out is that the studies that are out there generally follow the time from the development of symptoms. And I, I made up this term, it's probably not epidemiologically correct. But an anchor age, you know like some specific age that you could say that everyone who at and then follow them from that point, which of course for newborn screening would

be critical.

So we came up with a way to address that. And I will at least to some degree, and I will tell you what that is after lunch. Sorry.

Any questions, I'll be milling around here, so.

CHAIRPERSON BOCCHINI: Okay. Alex, thank you for getting us started in a really good way. And though we'll break for lunch and be back promptly at 1:15 to begin the rest of this discussion. Thank you.

(Whereupon, the above-entitled matter went off the record at 11:58 a.m. and resumed at 1:17 p.m.)

CHAIRPERSON BOCCHINI: All right. We are ready to start the afternoon session and we'll start by roll call. So we'll go down the list, we'll start with Don Bailey.

MEMBER BAILEY: I'm here.

CHAIRPERSON BOCCHINI: Jeff Botkin?

MEMBER BOTKIN: Here.

CHAIRPERSON BOCCHINI: Coleen Boyle?

MEMBER BOYLE: Here.

CHAIRPERSON BOCCHINI: Melissa Parisi?

MEMBER PARISI: Here.

CHAIRPERSON BOCCHINI: Kellie Kelm?

MEMBER KELM: Here.

CHAIRPERSON BOCCHINI: Fred Lorey?

MEMBER LOREY: Here.

CHAIRPERSON BOCCHINI: Dietrich Matern?

MEMBER MATERN: Here.

CHAIRPERSON BOCCHINI: Steve McDonough?

MEMBER MCDONOUGH: Here.

CHAIRPERSON BOCCHINI: Kamila Mistry, on her way, okay, and, Joan Scott?

MEMBER SCOTT: Here.

CHAIRPERSON BOCCHINI: Alexis Thompson, on her way.

(Off the record comments)

CHAIRPERSON BOCCHINI: Cathy Wicklund?

MEMBER WICKLUND: Here.

CHAIRPERSON BOCCHINI: Andrea Williams?

MEMBER WILLIAMS: Here.

CHAIRPERSON BOCCHINI: And Debi Sarkar?

MEMBER SARKAR: Here.

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

(No audible response)

CHAIRPERSON BOCCHINI: Not yet. Beth Tarini?

DR. TARINI: Here.

CHAIRPERSON BOCCHINI: Joseph Biggio?

MR. BIGGIO: Here.

CHAIRPERSON BOCCHINI: Debbie Badawi, on the phone. Okay. Susan Tanksley?

DR. TANKSLEY: Here.

CHAIRPERSON BOCCHINI: Chris Kus, on the phone.

MR. KUS: Here.

CHAIRPERSON BOCCHINI: All right, Chris. Adam Kanis, on the phone.

MR. KANIS: Here.

CHAIRPERSON BOCCHINI: Natasha Bonhomme?

MS. BONHOMME: Here.

CHAIRPERSON BOCCHINI: Ed McCabe?

DR. MCCABE: Here.

CHAIRPERSON BOCCHINI: Cate Walsh-Vockley?

MS. VOCKLEY: Here.

CHAIRPERSON BOCCHINI: And, Carol Greene?

DR. GREENE: Here.

CHAIRPERSON BOCCHINI: All right. Then, Alexis, caught up with her pocketbook.

Okay. All right, so with that we're going to continue the presentation and so I will turn it over to Dr. Kemper.

DR. KEMPER: So thank you very much. Before I continue where we stopped off with the

presentation there were two interesting questions and issues that were brought up with me over lunch that I thought I would share with everyone.

First, there was this question about if this is a single gene disorder why is there so much variation in how the phenotype presents and I think it's fair to say that this is still an active area of investigation.

And both Dr. Sue Berry and Dr. Ed McCabe made some good points about there likely being, you know, promoter genes as well as environments and epigenetic factors that have yet to be sorted out.

But, hopefully, you know, in the future that will be done. Carol Greene got all excited when I said that so I don't know if there's --

DR. GREENE: I just want to say there is nothing unusual about that. Lots of single gene disorders have that much variability.

DR. KEMPER: Okay. Well that's true, but, and like those, but that addresses the question about why that might be.

The other issue which was substantive for the conversation today is around, I was asked about the availability of transplantation and that really gets to several different questions.

So one is just accessibility of centers that can do transplantation. Of course, there are, you know, a relatively limited number of Centers of Excellence around the country that can do stem cell transplantation and that, you know, to sort of move forward, obviously, there need to be partnerships developed to be able to provide that service.

But I think probably the bigger question that this is really getting to is, you know, for how many people will there be a match. And so I did ask an expert in transplantation based on her experience, you know, where would this lie.

In terms of siblings she said that there would be a one in eight chance that a sibling would be a good match and then, of course, she wouldn't want to transplant someone if that individual also happened to be a carrier, or a heterozygote, so you

can see how that would decrease it.

And then if you just go out looking for a match in the sort of broader registry that's out there it really does fall down by race ethnicity with around 15 percent or so of people being able to find a good match if you are African-American.

And that's where umbilical cord transplantation comes into play because you can get away with a lesser match. And the number that I was given, again, this isn't from any evidence review or any other work that we have done, was that there would be in excess of 90 or 95 percent of the people that you could find with core blood transplants that would work.

Again, this is based on the expert opinion and I don't have data to bear that out. Were there any other like key questions like that before I dive back into the report?

(No audible response)

DR. KEMPER: Okay. Hearing none let me just recap our last slide because it's going to

provide the context for where we are going.

So if you remember we talked before about that the case series studies that are out there, and there are numerous, said if you get transplanted with a Loes score less than eight, nine, or ten, you know, depending upon the study, your outcome is better but it doesn't directly get to the question of whether or not transplant, or whether or not identification presymptomatically leads to improved outcome.

So let's dive into this a little bit more, right. So, again, to be clear, it looked like outcomes were better if you get transplanted when your Loes score is below a certain threshold.

But the bigger question is, you know, what happens with presymptomatic identification? So the solution that we came to is actually, you know, mirrors the public comment period.

We wanted to compare outcomes of cases that were identified based on the developmental clinical symptoms, so these are cases that would be

detected clinically compared to cases that would be identified through family testing.

So, you know, a relative of someone who was identified as having adrenoleukodystrophy and through extended family testing, you know, that they found out that this other person had it.

And our thinking about it was to be really be agnostic to treatment, so regardless of what happens the question is does identification in the presymptomatic period lead to a benefit of knowing and for this we're about to present we were really focusing on boys with ALD and further restricted to this childhood cerebral ALD.

And one of the things that I'd like to point out, and K.K. and I were talking about this during lunch, is that, you know, these data generally happen after but not analyzed this way.

So, for example if you look at these data that show the differences in neurocognitive outcome I was able to find out that five of these subjects were identified through family testing and the

other were identified by symptoms.

Now which five they are, I don't know, but that was sort of our background thinking before the analysis I'm about to show you. Dr. Tarini, you had a question?

DR. TARINI: Beth Tarini, AAP. A quick question, Alex. When identified through family, is the child more likely to get a bone marrow transplant before showing symptoms or signs like they would on that protocol? Is the trigger point basically earlier?

DR. KEMPER: So that was part of our question. So we really didn't know, you know, if you identify these kids presymptomatically are they getter earlier transplants and are they getting them at a lower Loes score was part of our question.

Again, you know, what happens to the presymptomatically-identified kids is exactly the kind of question and, of course, you know, we heard before in the public commentary period about people sharing their own family stories about this, but

this was a way for us to particularly get to this issue.

So we were able to identify two sources of data. One was data from a single- center, and this was described in the report and provided by Dr. Eichler, who is at MGH, and he provided us data on 30 subjects who were treated between 2006 and 2015.

17F is identified through extended family testing and the other 13 because they were identified based on symptoms. Now although there were, we started with 30 subjects and we only had outcome data on 19 subjects.

And the reason that we don't have it on the other 11 is that these are children who are enrolled in novel treatment studies and they were concerned that by providing us the kind of data we wanted that it would un-blind their studies. So that's why we had that drop off, okay.

Now, in terms of transplantation three of the seven family-identified individuals received transplants, okay. One of them, at the

time we got the data, was undergoing evaluation, and then three, I neglected to mention this before when I was talking about the natural history of the childhood cerebral form, is it's been estimated that maybe as many as 10 percent of individuals with the childhood cerebral from will have what's alternatively referred to as arrested or self-halted disease.

So their Loes score is progressing and then all of a sudden for whatever reason it stops for a period of time and they can predict who is halting and who is continuing to progress based on other MRI findings in terms of where the contrast is enhancing.

Again, that goes beyond my level of knowledge not being a neuroradiologist, but they use looking at certain areas as a signal that the disease is progressing.

So three of the seven in the family group had been transplanted and 17 of the 12 in the symptom group were transplanted. The four of them that

didn't get transplanted had advanced disease and one of them had this, arrested or self-halted disease and is continuing to be monitored, okay.

Now in contrast to that we have 59 subjects that were gotten from a multi-center database, so there is a company called Bluebird Bio that's collecting data from different treatment centers as they are working on developing novel treatments.

And so what I can tell you is that the 59 subjects here do not overlap with the subjects in the single-center. The single-center didn't report data to this other, you know, it's not really a registry, but this database.

So in that there were 25 boys who were identified based on extended family testing and 34 after they developed symptoms. All of the individuals in the multi-center database I'm about to talk to you about received transplantation, okay.

So, again, you know, these are not, you

know, this is not a population, you know, based registry, but it is a sample of individuals who have gotten treatment. Dr. Greene?

DR. GREENE: Yes, and it was implied by something you said on the previous slide, but so there was a sense that if you picked up because of your family as opposed to your symptoms that you are presymptomatic.

This slide makes it clear that's not true. There is a chance you are presymptomatic, but it looks like four of the seven of those picked up in families were already symptomatic.

DR. KEMPER: Well, so it gets --

(Simultaneous speaking)

DR. KEMPER: This is like a level of nuance that I can't tell you, but I'm about to go and show you a little bit more detail, but I can't tell you how long they were followed before they became self-halted or the degree of their involvement. So, you know, these are data over time.

DR. GREENE: And then for the next slide, so you are about to compare the outcomes after transplant of the ones picked up familial and the ones picked up symptomatic, but how many of the ones picked up in the familial identification were symptomatic when they were picked up?

DR. KEMPER: Okay, hold that thought. Hold that thought, we're going to get there. All right, so first let's just talk about who is in the data that we were able to get.

So, you know, it doesn't really compare across because it, you know, that doesn't make a lot of sense because, again, these are different populations, but just to give you a sense of who they are.

We asked for the first available Loes score for individuals, even if the Loes score was gotten before they got to the center, okay. So in the single-center group the first available Loes score was zero, right, so these were individuals detected through extended family testing who, at

least by the Loes score, had no cerebral involvement versus the symptoms group.

They were picked, again, the median age was seven, and their Loes score was 12. So, you know, it was substantially greater. Now if you go over here in this multi-center group, too, you can see it's four versus 7.5.

The median age of the first Loes score though, interestingly, it overlaps and, again, these are all, you know, such small numbers. I don't like to put too much weight into the whole thing.

If you look at the most recent Loes score that was available for the family detected group it was ten years of age versus the symptom group was 11 and you have a Loes score of three versus 12, okay.

So remember that's, you know, significantly higher in terms of the clinical impact and in the other database it was 5.75 versus 13.

And I'm basically sharing with you we got the raw data that we could get, but I had very limited information on exactly how people got to care and, you know, what led them there and stuff like that.

I do have some outcome data though. And so in the single-center trial I was able to get a combined outcome. This is, you know, a very blunt outcome of being alive and communicative and ambulatory.

So if you weren't communicative and ambulatory then in the survival curve you dropped out and otherwise if you were surviving or communicative and ambulatory you were in, okay.

I appreciate, and I owe Dr. Bailey, this is like the, you know, a very blunt description of neurocognitive outcome, but we asked and this is what we got, okay.

And I will say again that this is the first time for a particular evidence review that we've had to go to the well because the data about

outcomes from presymptomatic detection just hadn't been published.

So you can see the survival here, at least, you know, within this cohort, you know, everyone did well and that there was this, you know, dropout from the individuals who were detected through symptoms.

You know, these pink lines here are the, or the pink area is the 95 percent confidence interval because we couldn't draw a confidence interval around here because there wasn't sufficient variation.

With that being said, you know, it's pretty easy to do statistics and generate P values and confidence intervals and stuff like that, but, you know, statistics only help with, you know, understanding the impact of random error.

They don't tell you anything about symptomatic bias, so the degree to which you find this compelling is the degree to which, you know, you believe that this more broadly representative.

Can I share the next slide and then go to your question because I just want to show this is the multi-center study so the outcome here, again, was only survival and you can that there was this drop off for the ones that were detected through symptoms versus the ones that were identified through symptom development.

So symptom development here, family detection here, okay. So do you want me to like tell my limitations or do you want me to answer your question? Why don't you go ask your question.

MEMBER BOTKIN: Well, I just want to be reminded of the treatment status of the single- site kids in that graph.

DR. KEMPER: Okay. And I didn't tease them out separately although it's written in the report. Three of the seven in the family group got transplanted and seven of the 12 in the symptom-detected group did it.

And, you know, from my perspective the question that we were trying to answer is what's the

value of knowing early, not any, you know, we weren't wondering about, you know, adrenal, you know, hormone, you know, whether or not they were given, you know, had adrenal insufficiency or being treated for that, whether or not that got transplant, whether or not they got OT or PT or, you know, whatever it is that the affected kids are to get.

The question was really just is there something about knowing. In the presymptomatic period does that lead to a difference in health outcomes? So that's where that came from. Does that make sense?

MEMBER BOTKIN: It does. I just want to be clear on this graph those are kids who are both transplanted and untransplanted, right?

DR. KEMPER: This is regardless of what happened. And, again, I didn't put slides on this together but if you want to go more granular it's, I tease that out in the report or I could, you know.

I mean I have to say it's a very, the

Excel table that, you know, I sucked into my analysis program, there are not that many, you know, there are not that many rows and there are not that many columns, so, you know, we could look at it some more, but this is pretty much as far as we could take it in a meaningful sort of way.

So, again, remember this is only boys that had the most severe form, the childhood cerebral form. It's a small select number of patients with, you know, a variable follow who took care of that in the Kaplan-Meier analysis.

We don't have much, getting to the point that you talked about the treatment or the disease. Of course, it would be nice to know more about functional status.

You know, could we have pushed and maybe gotten more? You know, again, it took a long time to get the data that I am presenting now and, you know, maybe we could've gotten more, but at the end of the day, you know, these numbers are small just by nature of it being a rare condition.

So it may not, and this gets back to something that I think Dr. Boyle has pointed out before, that it may not detect the full spectrum cases that would be detected through newborn screening.

So this is how I would summarize this, okay. So there is no direct evidence about the benefit of pre-symptomatic identification of adrenal insufficiency, we've talked about that before.

Stem cell transplantation improves outcomes and if you get treated with a lower Loes score it's associated with better outcomes. Now if there's like a magic Loes score below which is better, you know, we can't directly answer that, or below which is best, right.

So we know that if you get transplanted with like an eight, nine, ten, depending upon what the study is, certainly you seem to have worse outcomes, but if there is like a magic number where that differential appears we don't know that.

But it certainly does lead to better outcomes with the lower Loes score. And then the unpublished data, the data that I just shared with you, suggests that identification through family testing leads to improved survival in late childhood, so we are able to follow the kids up through 15.

Again, remember there are lots of dropouts just because of the nature of the timing of when they were diagnosed compared to the detection after the development of symptoms.

So, again, it does look like, you know, there is this differential and, you know, for what it's worth it seems to hang together between the single-center and the multi-center data.

So what I'd like to do next is Lisa Prosser with her team at Michigan, has taken the data that I've just shown you and has propagated that into a decision analytic model to predict what might happen with newborn screening for implemented.

But before I call her up I'm going to give everyone a chance to talk about the evidence and then I think the -- why don't we ask, you know, go through the clarifying questions and then after Dr. Prosser talks about her work and then we have the APHL presentation by Mr. Ojodu that I'll come back again and summarize where we are with the evidence and how everything fits together and then we ask, you know, you have a chance to ask more, you know, thought provoking, difficult questions. Go ahead.

MEMBER LOREY: Alex, what's the upper range of a Loes score, or is there one?

DR. KEMPER: Thirty-four. That was such an easy one. I'm happy I knew that one.

MEMBER LOREY: That was helpful.

DR. KEMPER: Yes, thank you. Don't think I don't appreciate it because I do. All right, Dr. Greene?

DR. GREENE: On the first bullet, it may just be use of language, I don't have a good feeling

about no direct evidence about the benefit of presymptomatic identification of adrenal insufficiency.

I think you may want to expand a little bit on that and say what kind of evidence do you mean because there is plenty of clinical evidence that if you know somebody has adrenal insufficiency they don't die of an ear infection.

And you probably need some technical description of no published evidence of a certain level because I think --

DR. KEMPER: Right. So there's no high quality comparative evidence of children who are identified with adrenoleukodystrophy presymptomatically versus when they develop clinical symptoms in terms of outcomes from adrenal insufficiency.

And it's, again, not that we didn't try to find it, and we did also look for unpublished evidence directly to this. In fact, and I was told by one investigator who, and after getting kind of

frustrated with me said oh, actually it doesn't exist, you're right.

So I suspect, you know, when, you know, for everyone in this room, if there is a gap in evidence it doesn't mean that something doesn't work or that it does work.

It just means that in the evidentiary rules that we are held to it doesn't exist. And --

DR. GREENE: And you made that very clear at the beginning when you said it wasn't going to be about that.

My only discomfort is that on the summary slide it makes it read like there isn't any evidence of benefit and I would appreciate it, as a clinician reading that, if you would somehow restate what you mean by "direct evidence" in this context because taken out of context it reads very differently.

DR. KEMPER: Okay, fair enough. Other questions? Dr. Tarini?

DR. TARINI: This is Beth Tarini, AAP.

Yes, to follow on that and the comment you made that's come up in previous sessions when -- These are always rare conditions, nearly always.

We are always constrained by the number of subjects we have because these have not usually been ruled out in screening across states, so the idea is that we have small numbers and somehow that excuses us from the responsibility of trying to either get more data or, well basically get more data to understand it, is in my opinion a bit of a striking of responsibility.

I'm not saying you are doing this. I'm just saying that it's the point if we say well, it's one in 100,000, we're only going to get 40 subjects, then we're going to accept imperfect data and then perhaps we need to sort of reassess the standards at which we are going to apply.

DR. KEMPER: Oh, yes.

DR. TARINI: Now we'll have gaps and then the question becomes, on the heels of what Carol is saying, is the absence of evidence does not

mean that there is no evidence, but it also does not mean, is that there no evidence of benefit, it doesn't mean there's evidence of benefit.

And so each individual fills the gap in their own way. So I'm not clear, on the heels of that, Carol, what you would be more comfortable with it saying because I think on some level this gets at what do we do when there is the absence of that information, which is a recurring theme when you have a one in 100,000 incident, condition like this.

Because if that's the case then in some way we go down the slippery of slope of it will never be good enough and if you are one in 100,000 the bar is always going to be lower for you.

DR. KEMPER: Just can I add a bit of philosophy after receiving that. I think it's also important that we both as researchers and clinicians are careful in measuring things like this because we never know if we're going to be providing the quality of care that our patients and families deserve if we are not systematically

measuring these things.

So that's not really a decision point for this group, but I do think sort of an admonition for people who do research in the fields.

Okay, so -- Oh, that wasn't fast enough. Dr. Botkin?

MEMBER BOTKIN: I'm interested in hearing a little bit more of your thoughts about the ascertainment bias problem here between the symptomatic and the family detected and, you know, based on your knowledge of the granular nature of that data it seems to me it would be important to know --

Well, first of all let me say I think the differences are probably dramatic enough that you couldn't explain it by ascertainment bias, but it's still potentially a big problem and if the family identified ones are say 15 year olds who are asymptomatic, that are detected because their 2-year-old sibling became symptomatic that's different than the group of kids who maybe have

become symptomatic when they are two.

Okay, so maybe just looking at some of these data will help remind of where we are there.

DR. KEMPER: Yes. This is -- I mean your point is exactly right. You know, we want to make sure we're not comparing apples and oranges, which is really what you are getting to.

And, you know, we're never going to be able to completely resolve that issue with these data, especially because, and, again, going back to the point that I think Dr. Boyle was trying to make before when you start screening at a population level you just find a different spectrum of disease.

You know, I think the compelling aspect of this I think, and I don't want to insert myself too much, because I, you know, did go ahead and state all the limitations, but at least it hangs together.

It is consistent between these two different data sets and to the degree to which you can kind of like squint your eyes and look at the small case series and stuff like that.

It kind of fits together, but I agree with you. There is lots of moving pieces and confounders and stuff like that that are in there and that's just not something that, you know, we can resolve with the current evidence. Dr. Tarini, one more, it'll cost you.

DR. TARINI: Beth Tarini, AAP. So I completely understand that family screening is presymptomatic, symptomatic is symptomatic.

The one presumption that we could be making, and I'm not saying it's good or bad, is that newborns in the timeframe in which a child is identified from newborn screening to the time at which they develop symptoms under a monitor and protocol, or develop signs, that they are at the very point of identification transplanted as early as possible.

This does not take into account potential loss to follow up that could happen as a child undergoes continuous repetitive screening that is normal and the parent resolves the cognitive

distance by saying like, hmm, I'm not going to do another sedated MRI.

And so it predicates itself on the notion that the system keeps them in and follows them and they are not lost.

DR. KEMPER: Yes. So can I ask you -- It's an important point. Again, when we do our modeling and stuff like that we are just assuming an ideal world.

But these are issues that we're going to bring up and as a matter of fact I think, I'm going to make sure Dr. Prosser has time to really present these data because I presented kind of a qualitative picture of this and I think that after you see Dr. Prosser's modeling of how this would play out in the real world and then after you hear about the report of the systems that need to be put into place your comment will make more sense and then I'm going to kind of wrap things up when she's done.

DR. PROSSER: Okay, great. Well, thanks, Alex. So, well it says, what I'm going to

be doing in the next section of the presentation is going through how we use decision modeling to pull together, make the best use of the evidence that we have right now.

So we used decision analysis as a validated approach to evidence that this is, to be able to take advantage, especially in the case of newborn screening and we do have very small sample sizes in some areas in which we don't have any direct evidence that we can create assumptions and -- Is that better?

(No audible response)

DR. PROSSER: Okay, great. And so we could include assumptions into the model to fill in the gaps where we don't have evidence based on what we believe to be true based on our expert input and to create ranges to estimate population level health benefits.

But part of the process in creating the decision model also requires us to explicitly identify all of the assumptions and can also

highlight some of the key areas of uncertainty, and we'll see that in some of the results going forward.

So we used a computer simulation model to evaluate outcomes for a hypothetical newborn cohort of four million that undergoes universal newborn screening for X-ALD compared with clinical identification.

In creating model, as Alex mentioned earlier, we consulted with our expert panelists at three separate times, both in terms of creating the initial structure of the tree, it's always an iterative process in pulling together a decision model like this, identified a number of key health endpoints.

We ended up with a number of cases identified and a number of deaths averted by 15 years of age as our final endpoint. At the outset of this process we had a whole long list of possible outcomes that were identified by the Advisory Committee, by the Evidence Review Group, and by the experts as key outcomes for considering this

decision today.

But there was not enough evidence to model many of those intermediate endpoints that we would have liked to have looked at, including some of the more subtle neurocognitive outcomes.

So this slide shows the schematic of the final decision model that we used. So each of these boxes represents a health state in the model, so we have hypothetical cohorts of newborns, four million in each arm that go through newborn screening or go through clinical identification.

They go through a screening process, so following across the top part of the decision model, so a newborn can have an abnormal screen on the first and second tier.

If that is positive they'll move on to confirmatory testing. Coming out of confirmatory testing they would then get resolved into one of four separate categories that are listed here.

And, again, we developed this model in the context that the target for newborn screening

was to identify CCALD, and so while we provide estimates of the numbers in these other categories we haven't modeled any long-term outcomes for, for example, female carriers or other disorders.

So for those newborns that are identified with the ABCD1 mutation they then face a probability of either being identified with CCALD with adrenal insufficiency only, and it's important to note that in an earlier iteration of the model we did try to tease out different subgroups of newborns that had adrenal insufficiency and CCALD separately from those that just had CCALD, but we weren't able to do that based on the data.

So it's important to note that this group in the model includes both newborns with CCALD with adrenal insufficiency and without, and then long-term outcomes is whether they survive or die, and these are 15-year outcomes based on the data that Alex just went over from both the multi-site study and the single-site study.

And just to go through, this box here,

so, again, there will be a cohort of newborns with the ABCD1 mutation that's asymptomatic at birth and so these are newborns that there had been a lot of questions earlier during the evidence review, you know, clearly at this point we don't know what is likely to happen with these particular cases, that some will have adult onset, but some may remain asymptomatic.

So just showing the other sub-model, which models clinical identification. Again, we have three primary groups and so these are patients that are identified through clinical identification so we only have two categories here, but, again, we are comparing the number that identified with CCALD and here we are specifically looking at childhood cerebral ALD, adrenal insufficiency, and adult onset, again, trying to model the 15-year outcomes for those two groups.

And let me just pause here and ask if there are any questions about the structure of the decision model. All right.

MEMBER MCDONOUGH: Steve McDonough. Is there any information or estimates on how many children with adrenal insufficiency will die without, prior to being recognized?

DR. PROSSER: So that's a good question and when I get to the final results we'll be able to see where those cases might be, but we didn't directly try to model that outcome. Any other questions? Okay?

DR. GREENE: I think I understand. You are looking at the outcomes of that individual case and in neither scenario are you looking at the potential impact on outcomes of family members?

DR. PROSSER: That's right. So thanks for that clarification. So this is modeling a cohort that's not at higher risk for X-ALD and so excludes any family members of identified cases. Other questions?

(No audible response)

DR. PROSSER: Okay. So in terms of the modeling assumption, so all of the data going into

the model were based on the categories of evidence that have been identified in the evidence reviews.

So for the screening portion of the model the screening projections were based on New York data. Other model inputs were derived from the evidence review and supplemented by expert panel and we made some assumptions where we didn't have any data, and I'll go through those when I walk through the results.

With the assumption that potential benefits of earlier treatment are uncertain but could improve survival and improve cognitive outcomes, although we're not able to model any of the cognitive outcomes except for this very severe non-ambulatory, non-communicative state.

So just in terms of walking through these results, so starting with the bottom row. So the model projects that for a healthy annual newborn cohort of four million not at higher risk for X-ALD that under newborn screening annually there would be, the projections would be 143 newborns would be

identified with a range from 64 to 211 compared with under clinical identification a most likely value of 92 compared to a range of 64 to 132.

And I just want to clarify that these are not confidence intervals. We don't have enough data to estimate confidence intervals either for the input assumptions that are going into the model or our projections that are coming out and really should be viewed as a minimum and maximum range across that range.

So just going into these in more details, so the projection over the annual cases for newborn screening compared with clinical identification is projected to be 46 under the most likely scenario for both arms.

Twelve cases for adrenal insufficiency only, and remember there are cases of adrenal insufficiency in the CCALD category. And then here 85 cases of potentially adult onset, but these could potentially include cases that remained asymptomatic and this is where, you know,

consistent with the evidence, you know, we do not know what the long-term outcomes are likely to be for those cases compared with 34 cases of adult onset and, you know, these data are based on, you know, observed prevalence data and so these are actual cases whereas, of symptomatic adult onset, AMN.

And I just want to highlight here that, to respond to some of the earlier questions, you know, there is a range here that has a higher end under newborn screening for the number of cases that are identified.

We made a -- You have given that we don't have good numbers on, you know, what the long-term outcomes for identifying these cases of CCALD, you know, some of these may be cases that don't require transplantation and may halt in terms of their symptoms.

But, again, there may also be the case, given what we have seen of the instances so far from the New York pilot data, at least for the initial

one that was identified, that this could also potentially reflect a higher incidence detected under newborn screening due to cases that are either missed to cases that succumb to the illness before they are diagnosed and die before they are diagnosed, or cases that are not identified until much later in life or that never are, receive a diagnosis of ALD.

And I just want to draw attention to the ranges, too, that there is a higher upper end here that reflects the range of possible outcomes based on extrapolating from the New York data. Yes?

MEMBER MCDONOUGH: This is McDonough. Under clinical identification aren't some of those cases not going to be diagnosed or be diagnosed as something else because the doctors don't know what's going on?

DR. PROSSER: So --

MEMBER MCDONOUGH: Or that under adrenal insufficiency they may be diagnosed post mortem, the child has already died, figure it out

afterwards that the child had ALD if the child had acute illness and died and wasn't diagnosed beforehand, it was after the fact?

DR. PROSSER: Yes. So that's a good question. So we tried to use data that would most closely match cases that would have been diagnosed before death.

And so we did our best here to, you know, that's partly why there are ranges in there, because some of the data that we used it was hard to tell in the studies, you know, exactly when the diagnosis happened.

But this presents the best approximation to cases that would have been identified. And at least for adult onset these are symptomatic cases, so these do not include under the clinical identification projections cases, you know, that would not have been identified.

That's a good clarification. Other questions?

(No audible response)

DR. PROSSER: Okay. And so these two tables show the projected survivals using the two outcomes from the sets of studies, the single- site study and the multi-site study.

So, again, these are 15-year survival outcomes. So the top panel shows projected survival for cases that are ambulatory and communicative, so at 15 years it would be 46 are identified, under newborn screening the projected estimate is still, sorry, 46 is still 46 at 15 years of age compared with under clinically diagnosed.

Again, the assumption here, you know, is that these patients are treated according to recommended protocols, even if they are in the clinical identification arm.

So 46 compared with nine in the clinical identified cases, and so the number of cases of either death or non-ambulatory, non-communicative state of health is 37 for newborn screening compared to the bottom panel.

So these are -- Again, this is pure

survival. So this is from the multi-site study where the only outcome that we had was either survival or death, and so comparing those it would be 46 cases.

Again, all 46 were still alive, would be projected to be alive, the newborn screening arm compared with 28 under clinical identification.

And, again, it is important to look at the ranges, that there is a range of both number of cases averted as well as the number of deaths or being in a non-ambulatory or non-communicative state.

So just to summarize, so the projected health benefits for newborn screening compared with clinical identification using a model by 15 years of age is that there would be 18 deaths averted with a range of seven to 44 using a broader endpoint where we are looking at either deaths or cases of non-ambulatory, non-communicative state averted that the most likely value is 37 and ranges from 17 to 64 annually.

And I just want to highlight that, you know, our baseline assumption is conservative in that we are assuming that the same number of cases of CCALD would be identified under newborn screening compared with clinical identification.

But given the early numbers from New York State as well as what has been observed with other disorders is that that could be higher due to cases that could potentially have been missed in the absence of newborn screening.

And so that's where the ranges are important to try to represent what that uncertainty could look light and also to highlight that under certain scenarios the additional number of adult cases identified is projected to be as high as 76 cases.

So questions before I turn things back over to Alex? There's a question, go ahead.

MS. SHERWOOD: Janis Sherwood, Fight ALD. I just wanted to make a comment and I think that it's very important to note that the babies

that are identified at birth have the benefit of lining up a transplant hospital, a donor, finances, care for the other children, all of those things that we didn't have an opportunity to do with my son because time goes very quickly once you are identified because you are symptomatic.

It takes a month to get the referral to the typing to see if you can be a possible donor or it takes another month to find out if you have somebody in the registry, it takes a month to find out if you can go through the neuropsych testing, and so on and so forth.

So I think it's a very important thing to note that that eats up valuable time if you have to pull all that together once they are symptomatic.

DR. PROSSER: Yes. All right, thank you for that comment. And in addition to that I think it is important to note that our model is modeling the health outcomes, you know, that we have not been able to evaluate any changes in costs in either direction.

You know, that's not part of the assessment here either. Yes?

DR. OSTRANDER: Robert Ostrander. Did you project any of the complications of the treatment in any of this, or it may have gone by me, but, I mean that's always the decision, is the number needed to harm and I didn't pick up on that?

DR. PROSSER: Yes. So that's a really good question. So we have not incorporated in here any potential adverse events or complications of treatment.

We used the data directly from the two sets of studies, so like to the extent that those were included in there if they affected survival or, you know, the probability of transitioning into this severe non-ambulatory, non-communicative state then, yes, they would have been included.

But since we are not modeling any of the intermediate outcomes we wouldn't have captured that. Okay, great. Well, thank you. So I'm going to turn it over to Jelili Ojodu.

(Applause)

MR. OJODU: All right. I'm going to continue the momentum that has been started here with Alex and Lisa.

Good afternoon, everyone, I am Jelili with APHL, just a quick overview of my presentation on the public health system impact for X-ALD.

I'll be giving a short background, our role from the Association of Public Health Laboratories, the methods that we use to collect information from State Newborn Screening Systems and some of the results and a summary of the information that we collected.

So recommendations on adding conditions to the recommended uniform screening panel come in two-fold. You've heard Alex and Lisa talk about the certainty of net benefit.

I am going to be focusing on the readiness and feasibility of adding a new condition to State Newborn Screening Panels and the implications of all those as we move forward.

So we have some definitions here. We have defined readiness as follows. So for a State to be ready or a Newborn Screening Program to be ready they would be able to bring on the addition of a new condition to their own core panel of disorders and implement that within a year after the authority to screen has been in place already.

We define developmental readiness in that most states or Newborn Screening Programs could implement, again, with the authority to screen, and I'll talk a little bit, actually a lot about the authority to screen, within one to three years and then for states that, states will be unprepared to bring this aboard when most states will not be able to bring this, or implement even with the authority to screen after three years.

So this is how we define competence of the feasibility and we had, I think from, if you remember from our previous presentations on effectiveness of the public health impact that we developed over the years we've narrowed it down, at

least the feasibility of adding new conditions to making sure that there is an established test that picks up, you know, most of the condition and the test is actually available, a clear approach to diagnostic confirmation if possible, and then an acceptable treatment plan and then making sure that there is an established approach to long-term follow up. That's what we define as feasibility.

So why is this all important? I guess I could start off by saying we collect, or we want to try and get as much as possible, real life data, so we are sending a hypothetical -- Well, let's just go back.

Logical, hypothetical data surveys or questionnaires in the form of interviews or electronic surveys to State Newborn Screening Programs to better understand what helps either facilitate the addition of a new condition to the Recommended Uniform Screening Panel, or a challenge or a barrier.

And, you know, we have heard a number

times a number of folks talk about the fact that there's only one State that screens for X-ALD, and so, you know, keeping that in mind, especially thinking about population screening.

You know, we are asking states to be able to give us information on a condition that, you know, most of them are not screening for and, you know, how it would play out after they have the authority to screen from, you know, the folks above them, and then try a little bit to evaluate the opportunity costs as we move along.

So we developed a fact sheet for State Newborn Screening Programs, and I have a number of people to thank. It would take too long to do all of that, but you know yourselves. Thank you very much for helping us, most especially the State of New York for providing information --

(Off the record comments)

MR. OJODU: I have been called Alex a number of times. So, yes, we developed the fact sheet for State Newborn Screening Programs to be

able to better understand, you know, all of the activities and challenges and, you know, facilitators that you've heard from the one State that screens for X-ALD at this point in time.

The fact sheet, which is also included in your packets, also included the incidents of the condition, you know, screening methodology, resources, capacities and personnel, QC, short-term follow-up treatment.

Just something short, straight to the point that gives them information about a condition that most of them are not screening for.

We also provided a webinar to everyone, mostly in the State Newborn Screening Systems, to better understand how to respond to this logical, hypothetical survey that we sent out to them electronically and in the form of in depth interviews.

We surveyed 53 states, 53 states and Territories I should say, and did in depth interviews, that's phone interviews, with four

states, the four states that either have a mandate to screen and are screening, or have a mandate to screen and are planning to screen for X-ALD in the near future.

So, you've heard a lot about New York, the legislative mandate to screen and the population screening for the State of New York. There are three other states that also have legislative mandate to screen for X-ALD that are not screening for X-ALD at this point.

And so these are the folks that we called in the in depth interview and the results are as follows.

So challenges, obviously, from the State of New York that is currently doing newborn screening for X-ALD, we heard a bit about this but I would also reiterate that validating the assay took a little bit of time.

Certainly, determining how to multiplex, which is always a good thing of the screening for X-ALD with other lysosomal storage

disorder was a challenge that I think they were able to overcome.

Adjusting the cutoffs, also to make sure that we capture as many of those presumptive positives was also a challenge and also resolving the follow-up related issues.

I don't think I need to go too much into that. I think Alex and Lisa talked, especially Alex, in the asymptomatic males and the secondary targets there.

We learned a great deal from the State of New York and the factors that aided them in the implementation of X-ALD in their State.

Luckily, they were able to develop consistent communication and, you know, they have a really good relationship with a number of their specialty centers, healthcare providers, and, I guess, as I noted earlier, the idea and notion of being able to multiplex this with LSDs that they are already screening for in Krabbe and Pompe also helped in them not actually needing to procure new

equipment for this particular condition.

And then having the resources and the authority to screen, obviously in place from their state, was major facilitators in bringing on X-ALD.

As part of the in depth interviews that we did with the states that have a mandate to screen but are not screening we got some more information from them as well.

It's noted here and there is more information in your packets as well, California has a mandate to screen. Screening is required once it's added to the RUSP, and I'll just put an asterisk there.

There are a number of things that have to come into play before they actually screen, but the timeframe to screen the X-ALD and moving forward is not specified at this time.

It's not required to be added to the RUSP in Connecticut, which had a mandate to screen in 2013. They, obviously, have to develop and validate the assay that they are going to use or

maybe get an FDA-approved kit for X-ALD.

And then there has to be availability of necessary reagents and tests and there is not a timeframe to fulfill this. Obviously, a number of things have to go into play, and I'll talk a little bit about that later.

And in New Jersey they also have a mandate to screen. It doesn't have to be added to the RUSP. It has to be all of those things noted there.

And I think in an ideal world with everything being in play that they may be able to bring this on six months after they address all of the other concerns, but after it's added to the Recommended Uniform Screening Panel.

So these are challenges from states that have a mandate to screen but are not screening.

Obviously, the idea of making sure that there is a realistic timeframe to bring a condition aboard, whether or not it's been added to the Recommended Uniform Screening Panel, making sure

that they have the necessary time to work with the neurologist, which will be a first time for screening for a condition in newborn screening, referral process, tracking patients, follow-up issues, availability and validation of the test, and none of these states have higher increases. It's doing more with less.

In reference to facilitators that will help, I think it's similar to what I noted for New York, whether it's the availability of training opportunities, national training opportunities, and those federal partners that have funded those kinds of things, thank you very much. It's going to be needed especially now.

The adequate clinical and follow-up data, the addition of the condition -- so, you know, I think the addition of a condition, regardless of whatever the condition is, into the Recommended Uniform Screening Panel is, obviously, an impetus for states to add a condition in their states -- in some states.

And then the insights that they get from other programs, and so we have -- I can't remember who noted it earlier, but, certainly, a passionate community that shares information and insight from the folks that have already started to screen is invaluable.

And the adequate time to screen, you can't just turn on the switch or expect to add a condition and start screening almost immediately, although it's been the case recently.

So now I'm going to talk a little bit about the survey that we did -- electronic survey that was sent out to State Newborn Screening Programs and the idea was that they would share this with everyone in their Newborn Screening System, not just the lab, not just the follow-up, the clinicians and everyone who had to do something with this particular condition to make sure it was successfully implemented.

I noted that we surveyed 53 states and territories. We got a response rate of 70 percent,

so approximately 37 of them I think responded.

Twenty-seven State Newborn Screening Programs, six Newborn Screening Programs that either contract out to a regional or commercial lab, and then the four State Newborn Screening Programs that we did telephone interviews, in-depth telephone interviews for -- were excluded from responding to this long survey, long, important survey.

All right. So we asked the following questions and the survey tool is also in your packet. For this question we ask, if ALD was added to the Recommended Uniform Screening Panel tomorrow, how long will it take to get authorization to screen for ALD in your state?

This is the responses that we got. Approximately 61 percent of the states said it would take a year to three years after the authority to screen to add or to implement ALD in their state.

Another 24 percent, or a quarter of the states that responded, said it would take more than

three years.

For this slide we asked the question, please select the top three challenges related to ALD implementation. Screening test, short-term follow up, the highest number of challenges, long-term follow up, availability and support of ALD specialists also followed, and treatment.

A little busy slide here, but, let's see, the question was please indicate your program's readiness to implement screening for ALD by evaluating the following responses that we gave them.

As I said it was a long but necessary survey and wanted to make life a little bit easier as the State Newborn Screening Programs are responding and so they gave a wide --- varying responses to what we presented here.

Availability of treatment centers, developmental follow-up protocols, necessary laboratory technical expertise, you need to have the right LIMS system when you are adding a new

condition, and then figuring out the screening approach.

And I think we've heard a good amount from Alex in reference to the New York program, but there are a good amount of states that are not screening for the other conditions that can be used to multiplex for this particular condition, and so they have to figure that out as well.

All right. So this question here, a busy slide, sorry about that, but I just wanted to put some nice, beautiful teal colors in here.

To what extent do the factors below impede or facilitate the adoption of ALD in your Newborn Screening Program? The cost of the specimen, ongoing activities, whether it's the addition of other conditions that has been added prior to this new condition, in this case X-ALD, the cost of treatment, the cost benefit, and some states actually do cost benefit analysis for each condition that is being brought on, and the second to the last bullet point there is the ability to

multiplex with other conditions.

So significant barriers from State Newborn Screening Programs. Funding is always and almost -- the most important significant barrier. Funding for, you know, platform technology, assay, staff training.

The legislative approval to bring on a new condition. I cannot emphasis that enough in that there has to be a mandate, at least in a good number of states -- five minutes, thank you -- to be able to bring on this condition and they won't be able to do that without having the approval by someone higher than them.

Staffing, for the states that contract their newborn screening out to either a contract lab or a regional lab, it's important for that lab actually, or program, to do this screening or have the implementation for screening for, in this case X-ALD, before they can bring it on, and then competing public health priorities.

Facilitators' addition to the RUSP,

early detection and the benefits of that, the readiness of those contract labs in performing the test, and the advocacy activities that initiate and bring about, you know, the --- addressing all of the issues, not just addition of the condition but also, you know, funding and other factors that I've talked about earlier, plays a major facilitating role.

So, last, how long is going to take for states to be able to bring on SCID and what are those factors and how those play into their thinking here.

As you can see here, a number of Newborn Screening Programs are in purple. It's going to take them pretty much a year to three years to bring on the necessary staff to pilot and validate the test, to be able to procure the testing equipment, to be able to report out the full implementation of X-ALD in their state. The majority of them pretty much fit into that category in the middle there.

So, the strengths of the survey. I talked about the fact that it was -- we got 70 percent of the states to respond to this. I thinks

that's a good thing. We would like to have more states respond but they are busy actually screening for other conditions or other things in their newborn screening programs.

The fact that we provided fact sheets to State Newborn Screening Programs and webinars was a really good thing for states that weren't screening or are not screening for X-ALD and, you know, the fact that we also got real life experiences from states, or the only state that is screening for X-ALD helped not only us but the states that were responding to the survey.

Limitations are listed as below. This is hypothetical. These states are not screening. We are asking them questions that -- the responses in some cases are subjective, but it gives us a really good opportunity to understand real life, what it will take to bring these conditions on. And the limited data related to X-ALD, at least as it relates to newborn screening.

This is all assuming that states have

approval and funds have been allocated to screen for this new condition.

So most states, or at least 61 percent of the states surveyed, and two out of the three -- those that have a mandate but are not screening reported that it would take a year to three years to implement fully with the authority to screen for X-ALD and the allocation of funds, which may require a legislative approval or mandate.

And at best, from our description or definitions that I provided to you earlier, we believe that adding X-ALD to State Newborn Screening Programs is developmental ready.

In reference to feasibility, long-term follow-up plans will remain. The development of those kinds of activities remain an issue that states need to overcome before they bring it on. The late onset of the condition and picking it up in the newborn screening period, the length of tracking of the infants that are picked up through newborn screening.

And in summary the cost associated with adding a new condition, in this case X-ALD, continues to hinder the implementation of a new condition to the Recommended Uniform Screening Panel, in this case X-ALD.

States don't have funds, and newborn screening -- the lessons that we learned from New York has been very, very invaluable in providing how and --- the challenges and facilitators in adding a condition to the Recommended Uniform Screening Panel.

I'd like to quickly just thank Elizabeth Jones, the folks at APHL that helped develop this survey, the folks on the Condition Review Workgroup that helped also put together the survey, and, most importantly, State Newborn Screening Programs that provided us with the information. So, thank you.

DR. KEMPER: Don't run away.

(Applause)

DR. KEMPER: All right. Oh, do you have a question about the topic?

(No audible answer)

DR. KEMPER: Yes, go ahead.

MEMBER MCDONOUGH: Yes, two questions. One is when and if states that develop testing for Pompe Disease, which has been added -- recommended to be added on to the RUSP, how does that impact the need for equipment and staff, does it make it easier and can a state add ALD easier had they already done Pompe?

And the other question I have would be assist states if the federal government would provide some additional resources to them when we make a recommendation to speed up their time for screening?

MR. OJODU: I'll start with the second question. The funding opportunities, whether it's in pilot projects to State Newborn Screening Programs, is always very helpful in bringing on a new condition. We have seen it. We are scaled then for other conditions that have been added.

In reference to your first question, I

think it's very -- to be very PC about this, we focused mainly on what was the public health impact of adding X-ALD.

And even though there are other varying factors or variables that can affect the addition, either through multiplexing -- there are only, what, two states that are actually screening for Pompe right now, and it's just been added. We try not to --

DR. KEMPER: But if you are using tandem mass spec to screen for Pompe disease, and I guess I'm looking for Dr. Caggana now, maybe she's back there? No. You know, you can multiplex with it.

So if you are using the tandem mass spec platform for doing it then it's, you know, an incremental addition versus having to get new equipment, if that's what your question is.

I think there are competing ways of screening for Pompe Disease. Does that make sense?

All right, so everyone's still with me. This is a very high level, you know, we were at

30,000 feet before, now we're going up to the International Space Station.

As I think we can all agree, X-linked adrenoleukodystrophy is associated with significant morbidity and mortality, especially in affected males that stem cell transplantation can be an effective therapy for those with a cerebral form.

And the studies support that outcomes are improved when there is less cerebral involvement and then the unpublished data that we shared with you suggests that there is decreased mortality perhaps, morbidity in late childhood among individuals who are diagnosed through family testing compared to after the development of symptoms, and that would be the indirect path to benefits of presymptomatic detection.

Again, we talked a lot about adrenal insufficiency being common and it can be treated with replacement therapy, but, you know, I'm not going to revisit how to say this, but basically

there is a gap in evidence about the risk reduction related to morbidity and mortality from adrenal insufficiency related to presymptomatic identification.

We always have to balance this with, you know, the potential harms, including the identification of heterozygote females and the other peroxisomal disorders, so identifying things that are not targets of screening, the degree to which you consider that a harm or not depends upon the value that you put on detecting those things.

Individuals identified through screening may need --- you need to do follow-up within the certain course of disease, so, you know, you can either do this within a public health context and to ensure that there is a public health system that can track individuals over time or at a minimum ensure that individuals are connected to specialty centers and have the resources for that kind of follow-up.

I would hope that if it's done, though,

that it would be within some sort of public health overlook so that we can get the gaps in data that were needed so that we can improve the quality of care that people are getting, both children and their families.

Transplant is associated if you look across the studies with a risk of mortality, and, you know, we talked about that 5 to 8 percent number. The issue here is the degree to which you are exposing that harm, if you really are treating the cerebral form, you're just shifting it to an earlier period. So you are shifting the risk from later to sooner by initiating therapy early.

As Jelili spoke, most states anticipate needing at least one to three years to adopt screening once funding becomes available, and, of course, as I think everyone knows, you know, funding can be a challenge.

So I'm going to stop there and open things up to questions and then let Dr. Bocchini take things from there.

CHAIRPERSON BOCCHINI: Okay. Any additional questions, we'll of course start with the Committee, and then liaisons? Oh, okay, sorry, Coleen.

MEMBER BOYLE: Hi. This is Coleen Boyle. I had a question, something you didn't talk about and there may not be anything more than what's in the data, so there is just other unpublished data on the cord blood transplants, that abstract, which is the last part of your results?

DR. KEMPER: I just, you know, so I asked --

MEMBER BOYLE: Is there anymore information in there?

DR. KEMPER: There may be. Not that, you know, again, this was kind of a late addition because I was just trying to find out -- Are you talking about the availability --

MEMBER BOYLE: Yes.

DR. KEMPER: -- or the harm?

MEMBER BOYLE: Well both.

DR. KEMPER: Or both?

MEMBER BOYLE: Yes.

DR. KEMPER: So, again, this wasn't within the scope of the original review but I went back because it was, you know, sort of an obvious gap and so I --- you know, I'm like 93 and six-sevenths percent sure, for what that's worth, that cord blood transplants would be available for most individuals who couldn't find a match other ways.

And in terms of the risk of mortality, again, this was from one treatment center looking across all of the non-cancer indications for transplantation and, you know, sort of mixes in a -- you know, it's a heterogeneous group of people, some people who are probably more sick at the time of transplant and some people less sick and that kind of thing.

So, you know, it's somewhere in that ballpark. It's, you know, certainly not zero.

MEMBER THOMPSON: I just would question

the optimism about cord blood. There certainly are a number of conditions for which cord blood is not an acceptable option and we just don't seem -- we certainly see a disproportionate amount of graft failure with cord blood such that it really has not been a substitute for marrow I think is one consideration.

I think that the disparities in terms of availability of cords related to race and ethnicity can't be overstated because I do think that that still is very much a problem.

I think the third one is that we know that there are limitations. There is an absolute limitation in terms of the number of cells that one can usually obtain from a cord blood unit and the size of the recipient that certainly there really does seem to be an upper limit.

And so certainly children over about 30 kilograms are unlikely to actually be successfully reconstituted with a single cord blood unit.

DR. KEMPER: Yes. And even to add

another nuance to the whole thing, I was surprised to learn how much variation there is across banks in the number of viable cells that are available in cord blood banks.

MEMBER THOMPSON: Well I do think that that's --- the ability to actually search centrally through the National Marrow Donor Program has certainly helped that tremendously.

So to the extent that the information is available in terms of the volume of a given cord blood unit, that usually is available to the transplant center fairly quickly once an HLA match is identified.

DR. KEMPER: Yes, thank you. I agree with everything you just said.

CHAIRPERSON BOCCHINI: Natasha? Somebody give Natasha a microphone. Thank you.

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance. This is a question for Jelili in reference to, I think it was one of the earlier, very colorful slides, that broke down what -- the one

before this one.

DR. KEMPER: Is there another colorful one?

MR. OJODU: No.

DR. KEMPER: That was it.

MS. BONHOMME: I thought there were two. Maybe --

DR. KEMPER: There was that one --

MS. BONHOMME: That one. Okay, yes.

DR. KEMPER: This one?

MS. BONHOMME: Yes, I'm sorry. The previous one, sorry.

DR. KEMPER: Oh, I'm sorry.

MS. BONHOMME: I was wrong.

DR. KEMPER: It's okay, I'm here for you.

MS. BONHOMME: That one. Thank you. Now after all of that, actually I'm not sure -- but, so, you know, just looking at the example of the second one that says "Treatment Centers" for the caseload and that that's 49 percent of states.

Are you able through -- not just through this survey but through some of the other data that's collected through the repository, being able to look at that question based off of the percentage of babies born that could be served?

I don't know if I asked that correctly, but this is looking from, like this is 49 percent of states. Do we have the data around X number of babies born?

MR. OJODU: Great question. We did not do that. We hope to be able to do that in the future.

If State Newborn Screening Programs, as Marci presented this morning, once they start entering all of that information into the data repository I think we'll be able to get a good amount of the public health system impact information that can help supplement these kinds of questions that we ask any time a condition is being added to the Recommended Uniform Screening Panel.

Did we do it this time? No, we are still

in the process of collecting that data, but I think it's something that we plan to do in the future.

MS. BONHOMME: And, sorry, one more question. When you talked about having the authority to do this screening is that just from a legislative perspective or can you give a --

MR. OJODU: It depends on wherever a state gets their authority to screen, legislative or, you know, advisory committee. I mean different states have different ways of adding a condition.

Most states have, you know, there has to be their legislative mandate, because sometimes it comes with a fee increase, and so it has to go through a number of processes there, and then some states it's a little bit easier.

But that's all relative. Easier doesn't mean that they still don't go through the process of, you know, the variables that I talked about in bringing on a new condition.

Once they have that authority to screen then they'll take one to three years, according to

the folks that responded, to be able to bring on a new condition.

DR. MCCABE: Ed McCabe from the March of Dimes. I have a comment and then a question for Jelili.

We've been talking about cord blood banks generically. I just want to remind everyone that we're really talking about public cord blood banks, which are the ones that are accessible for anyone. So that is an important distinction I think.

And then for Jelili, the final bullet in the overall summary says that most states anticipate needing at least one to three years to adopt screening once funding becomes available.

My impression is that if we revisited this two years from now, it would still be one to three years, but you know this area better than I do so I wanted to get your response.

MR. OJODU: I think different conditions require different activities to bring it

on. I just described everything for X-ALD and the public health system impact.

We can talk about other conditions that's been added since the ACMG HRSA 29 conditions that were added in 2005. You will hear a lot about this during my presentation tomorrow, actually, on the implementation of those three conditions.

I think there are just -- it's a dynamic process of what states need to go through and I can't -- I don't know if I can actually say where we will be, if it will take another one to three years, if we come back after one to three years to look at where we are for X-ALD, but we can use other conditions that's been added as a good guideline of what may happen.

MEMBER THOMPSON: So along those same lines, and I think I know the answer to this, but I feel like I need to ask anyway.

So when you talk about this one to three year range I'm a little bit -- I'm struggling a little bit with the paucity of evidence for benefit

that we have beyond survival and it sort of --- the question I guess I would ask is, if we really are still saying that one to three years was a minimum, because certainly there were many that still had over three years before they would be ready, is there any expectation that information will become available in the next one to three years that would actually allow us to have more confidence that there really is benefit in terms of interventions for children who are diagnosed as newborns?

DR. KEMPER: Yes, let me take a stab at that. I know exactly what you mean, too, because the only really direct evidence that we have from there is the, you know, New York.

So if you would expect, you know, the boys, you know, a fraction of the boys that develop the childhood cerebral form, and then you need to follow them out for a period of time, I would suspect, although other people might feel differently, I do probably think more than three years just for the cohort that's been identified to

get treatment and then, you know, for the new cases that are accruing in there.

You know, Jelili and APHL do a great job with this survey trying to figure out where states are and stuff like that.

I -- you know, maybe this is echoing what Dr. McCabe's question is, you know, they say one to three years. I mean it's hard to really know what that means and I think of it more as like, you know, if they say it'll take a year or less then it's like a slam-dunk easy thing to do, one to three years is like they kind of, you know, have bought into the, you know, perhaps it's the right thing to do and, yes, we can do it, and then the more than three years just being like this is like so far like out of the zone of what I can do.

And it would be my hope then that, you know, again, you know, I can't predict if you guys are going to go for this or not, but the new funding mechanisms that have been developed to help states implement would get over those barriers, both just

operationally in terms of doing it but also being able to develop the data registries to understand whether or not all this activity is making a difference.

That's a really long-winded answer to your very short, easy question. I don't know if I answered it or not, but I think that one to three years might not be sufficient time to accrue enough cases.

CHAIRPERSON BOCCHINI: So let me, we need to go Committee first and then liaisons and then we'll go to the microphone, but I guess Kellie would be next and then Carol and Susan and then we'll go to the next one.

MEMBER KELM: Kellie Kelm. So one of the things -- since we're looking, talking about some of the unpublished data you have on the single site and the multiple center site, do you have any insight on why -- so the single-center site had a -- I know 50 percent of them were transplanted, but the multi-centers one, 100 percent of them were

transplanted.

DR. KEMPER: Yes.

MEMBER KELM: Do you have any insight on why there was that difference?

DR. KEMPER: My understanding, you know, and, again, this is all, you know, from my email that -- people have been sending me email -- is that the data that they collected were specifically around transplanted individuals.

So it was the data that was requested from each of the treatment centers, not, you know, any function beyond that.

Again, neither the single-center site or that multi-center site was set up to answer the questions that we asked them, which is why, you know, we don't have like, you know, very good symmetrical outcomes and, you know, why I can't comment on, you know, the individuals who didn't get transplanted.

I mean there's lots of stuff I can't comment on, but that's why.

MEMBER KELM: I just want to tack on real -- And I think Michele may have said this, but in terms of the centers that the New York kids are going to, is there -- they're leaving it up to centers to decide to how to follow them and to transplant them, so there isn't some, you know, since this is a new population that we're following and potentially transplanting as they develop, do we have any idea that are, you know, how they are going to do that or --

DR. KEMPER: You know, I would invite either Dr. Caggana to come up, because I don't want to talk for New York, or Dr. Kwon if you want to run up to the microphone.

Oh, there -- I can't see. Are you back there? There you are. Dr. Kwon's going to kill me. All right. I think you're -- It might be off.

DR. KWON: You even asked the question, I apologize -- Oh, hi there, Kellie.

Oh, I'm so sorry, I'm Jennifer Kwon, and I am a child neurologist from New York State.

And so if what you are asking is have we banded together in New York State to, you know, sort of set up a clinical outcomes registry to look at how we are following patients and collecting data I would say that, no, we're not there.

We have sort of a proposal that was put out by New York State that, as Beth Vogel said, they developed with Jerry Raymond, who is a child neurologist in Minnesota and an expert in X-ALD, and some of the metabolic centers to try to kind of get the short-term confirmatory testing, you know, off the ground.

But in terms of looking for the kind of data that you need to really -- to sort of like solidly say, yes, we have evidence of benefit for early screening we aren't -- as far as I know we're not in the process of collecting that data.

MEMBER KELM: Well my question was a little bit more -- I mean, obviously, you know, these sites are transplanting based on sort of current practice, but I mean do you think that's

going to change when we are identifying earlier? Or I mean, is there going to be some change in that, or do you think it's maybe the same or are you going to use sort of the -- the center is going to use the same process to decide to transplant?

DR. KWON: So currently when we diagnose, because we do have information, right, on individuals who present because of family history, so we diagnose them asymptomatically and we have a follow-up strategy and that follow-up strategy, I would say, is guided by experts, such as the ones that were on the expert panel.

And in general what we do is we follow MRIs along with experts. We look for evidence of disease progression, and then we also look for evidence that the disease progression is true disease progression.

I think that one of the things that hasn't really been alluded to is the fact that every one of us is conscious of the fact that we don't want to transplant someone who doesn't need a

transplant.

And so while it would be really easy to transplant all 3-year-old boys with X-ALD we of course don't do that, because some of them don't go on to develop cerebral forms or progressive cerebral disease.

So I would say that those protocols are in place. They're kind of understood. It was actually an interesting part of being on the Evidence Review Workgroup to realize how little evidence has been collected to show the benefit of early diagnosis when in fact it's considered common knowledge in neurology circles.

DR. GREENE: So one comment that is I think actually a follow-on to that, and to something earlier, and then a 2-part question.

The comment is that there was, in Jelili's excellent presentation, there was reference to some issues of, do we have the resources to deal with this? And I think we just heard, neurologists have standard protocols and

there is the question of, you know, do you have the neurologists to deal with this?

Well if you've got the neurologists to deal with the kids, the large volume of kids that we have who come out NICUs with brain injury and white matter disease and all sorts of other things, they are the same neurologists who are going to be dealing with these kids diagnosed asymptomatically or diagnosed symptomatically.

So they're going to be dealing with a very small number of kids, they are going to be dealing with two for every one that they would've picked up symptomatically. That is a tiny, tiny volume for any state's neurology. They've got no problem with that.

Speaking for metabolic, it's a small volume and the other team that you need is heme oncology and you had an eloquent description of, you know, thinking about the risks, but in terms of volume, if you've got access to somebody because you've got kids with leukemia and you have to think

about bone marrow transplant, I don't think that the volumes here are going to tax any of the necessary specialties, and those specialties are in place with all the caveats, but I don't think volume is an issue here at all. That's a comment.

My question is, thinking about, and I didn't have good enough web access, but the first --- the question goes to the evidence for benefit, and as the Committee is going to deliberate, you for good reasons didn't consider the possible benefit to the kids who would have -- the 10 percent who would have adrenal insufficiency.

One question is, did you look for the evidence of any publications or evidence of benefit to people, forget about the ALD, but just death with acute events in adrenal insufficiency when you are known to have adrenal insufficiency versus when you are not because I think that the ideology of the adrenal insufficiency wouldn't make any difference. Is there no evidence there either?

DR. KEMPER: Yes, I mean, you know, sort

of under our rules of engagement we try not to work by analogy because things are different.

And so what we know with ALD is that there is this, you know, indolent increase in, or I guess I should say indolent decrease, in adrenal function before they eventually hit this point where, you know, they are truly adrenal insufficient and at risk.

That's a lot different than say like, you know, the neonate that's had some injury and whose adrenal glands don't work. It's different because they come to attention different ways, and people are thinking about it, so in some ways that decreases the risk.

And so you could either under or over estimate the risks. So the rule that we operate by is when we don't know the answer we try to outline what we don't know and the magnitude of the problem.

So here, you know, there is a lot of adrenal insufficiency but the degree to which that adrenal insufficiency -- the absolute risk of that

leading to, you know, some bad outcome, we can't predict from the available data.

I mean certainly there is anecdotal, you know, case reports and that sort of thing, but not the population-level data that would be able to, you know, maybe give you a risk.

DR. GREENE: That's a fair answer, thank you. And I also realized I didn't say that we're also still talking about a small volume, I don't think that the endocrinologists would have any problem absorbing the few kids that would need to be monitored.

So would it be fair then to say that when the Committee deliberates that you can't put any number on -- you can't say whether there would be a benefit, or put a number on it, but is there any downside to identifying children at risk for --

DR. KEMPER: Yes, I mean, again, this is, you know, why you all get to sit at the big table and I don't.

So I don't want to be overly, you know,

be accused of overly influencing things one way or another, so what we are talking about is monitoring a child over time to find out if they adrenal insufficiency.

So there may be, you know, extra lab tests that are involved with that, and then at the point that they become -- you know, that their adrenal glands can no longer keep what their, you know, baseline, you know, cortisol requirements are, that they get replacement therapy.

So, you know, the downside is, you know, is there a risk that, you know, a child might get, you know, adrenal replacement therapy, doesn't need it? You know, probably.

Is there a downside to that? You know, those of you who are clinicians can comment on that, I don't want to impose myself on that.

DR. GREENE: And then the second part of the question is more for the Committee, is just, when you deliberate, you are obviously going to be thinking about the benefit to the child, because

that's what the evaluation was focused on, but it is still a screening for X-Linked Adrenoleukodystrophy and it could affect many, many more people with -- find people with Adrenoleukodystrophy besides that one individual child, which is what the analysis focuses on.

DR. KEMPER: Exactly right.

DR. TANKSLEY: Susan Tanksley, APHL. I first wanted to comment and then I had two questions.

So I wanted to respond in regards to comments or questions about the one to three years for implementation and -- you know, if we looked at it in two years, would it still be one to three years for many of those states.

And I think the caveat of, you have authority to screen and funding, is why you might see the same answer in two or three years if you looked at this again because those --- so, okay, I'll speak for Texas. So in Texas it's in our statute that if it's on the RUSP that we are required

to screen for it as funding allows.

So we have the authority immediately as soon as the Secretary signs the letter. However, we still have to identify the funding to be able to do whatever we need to do to implement the screening and sustain this.

And so I think that's why we see so little movement and many people are frustrated by that, but it's a reality of running a Public Health Newborn Screening Program, and so that was --

DR. KEMPER: Can I amplify that point, too? So, you know, a lot of times Jelili and I have been asked, you know, why the question is, you know, once funding is available? And that's when back in the day when all this was being developed, if you didn't put that caveat, then basically every state was saying never, in which -- you know, isn't particularly helpful. So, you know, it's hard to tease that out.

DR. TANKSLEY: Right. And so when you answer that as a State Newborn Screening Program

it's easier to get down to the other barriers, the other issues that have to be overcome if you can say okay, let's pretend that we have the funding, let's pretend we have the authority to screen, then what, then what are the other issues that you have to overcome and the funding will come eventually after there is approval authority if the state chooses to do the screening.

There are --- different states have different processes for that approval authority. And that was already stated, that it may come from a legislature, it may come from the advisory committee, it may come from an internal process within the health department. So that was my comment.

I did have -- I had two questions. So one of them has to do with the -- so for Alex, on the unpublished data, the family risk versus the symptomatic onset for the single-center and multi-center studies.

I was -- This may have been stated and

I may just be overlooking it, but is there a sense of what the, I'm going to have to call it the Loes score because I've heard it so many times, is there any sense as to what the Loes score was in the different study groups?

DR. KEMPER: Yes. So we have -- this is the first available Loes score which each site told me that it was the first one they could take out from each one, so we had in the family group zero versus the symptom group, 12 in the single-center one, and four versus 7.5 and then underneath there you can see the median age and the, I think I put in the 25 to 75 percent.

DR. TANKSLEY: Yes, I missed part of my question.

DR. KEMPER: Oh.

DR. TANKSLEY: So at stem cell transplant.

DR. KEMPER: Oh, at the time of transplant. No, we don't have that information.

DR. TANKSLEY: Okay. And my second

question is a New York question, and it has to do with the babies that have already been identified, and this may be a Michele question or Dr. Kwon or a Beth question.

But my question is, you know, do we have any indication of the status of any of those children? Have any of them exhibited any symptoms at this point as far as the adrenal insufficiency or an indication by MRI?

MS. VOGEL: Michele just stepped out, I can answer that. We've had one of each, one child who has already had some findings on their MRI and actually had a transplant at ten months of age and one child who has been on adrenal replacement therapy since six months of age, and the rest have been asymptomatic.

MEMBER BOTKIN: Yes, I think this was sort of a follow up to Alexis's question and maybe Susan's, too, and I guess, you know, we're going to be asked to make a recommendation on pretty thin data here shortly.

And let's imagine that we go forward with the positive recommendations. States begin to implement screening. Given the fact that we no longer then have a comparison circumstance, we've got historic controls, lots of limitations with those, but I wonder if it's possible there to think about how modeling might work.

Maybe this is a question for Dr. Prosser, could you model the conduct of screening such that we would know at some point whether we have made a good decision or not?

In other words, how much data would we have to collect from screening programs given the quality of the historic controls in order to draw any conclusions about whether this has been a successful program?

DR. KEMPER: Can I --- before Dr. Prosser gives like a much better answer than I'm about to say, I would say that, you know, there are ways to determine the value of information and whether you're going to go that way or not.

But the other thing is it's not like even if you were to recommend screening that all states are going to suddenly be doing it anyway, so I think that, you know, for example, if we look at like CF and SCID and stuff like that there's been an opportunity to find out whether or not the decision was right or not, but I'll let Dr. Prosser --

DR. PROSSER: Right, that was going to be my response, that --- assuming that there is going to be some --

DR. KEMPER: We are a good team.

DR. PROSSER: -- difference in terms of the timing with which different states implement screening that we would be able to, you know, especially if we could introduce some partnering with the states to be able to collect data in the interim period on the outcomes of those that haven't yet implemented screening to be able to do a comparison retrospectively, yes, we could absolutely do that.

MEMBER LOREY: I didn't mean to make

that noise. Well I think we can look to SCID implementation to see how that's going to draw out.

So we had, what, eight states in the first year or two after the recommendation and then slowly and slowly and now here we are five years out and there are still 25 percent who have not started SCID screening.

So was that your question, like comparing those that are screening versus those that are not?

MEMBER BOTKIN: Well that might be one way to do it, if you had equivalent data sets between the two, but you still have the ascertainment bias between the states who are screening and those who aren't screening.

So I guess what I am saying is if you assume a certain level of benefit for transplants for a certain subset of kids with the X-ALD then how many kids would you need to identify in order to demonstrate what's a convincing -- that you have indeed delivered the benefit that you are

anticipating?

And if it's a matter of saying well, you know, 2 million kids, once we get 2 million kids, whether they're all of California for four years or whether it's out of a variety of states might be irrelevant, but how many, at what point ought we see evidence that this has been a good decision or not based on what we are modeling to be the efficacy of the intervention?

DR. PROSSER: Yes.

DR. KEMPER: I mean it, I think that would be interesting, what you said, but I mean if you think about, you know, one case in 100,000 to CCALD, and it takes awhile for children to get to the point of either being detected clinically or to go through the pathway and need to get transplanted and if you use the rule of thumb of like, you know, three outcomes for each variable that you have in the model it quickly becomes overwhelming, and that's one of the advantages of modeling.

But still if you want to be certain it's

going to take quite a long time.

DR. PROSSER: Yes, right. And I would say that right now it would even be hard to try to estimate what sample size we needed given, you know, the sample that we have now. We just have, you know, what, 15 in one study and, you know, 30 in the other.

DR. KEMPER: That's, you know, rare disease.

DR. PROSSER: Yes.

DR. SALZMAN: Okay, great. A couple of things that -- at the risk of it being obvious, please indulge me. I think when the modeling was presented there was some flaws that underestimate the value of newborn screening and -- let me just draw attention to a couple things.

There was an unstated assumption that family identification equated to newborn screen identification and that, in fact, is incredibly wrong, because it's often identified when a kid already has a Loes score of like three or four.

I mean if you take -- again, it's just my family and it's anecdotal, but I had a son who was 1-year-old, he is now a healthy 15-year-old. My other sister had a son that was eight year old at the time that his older brother was diagnosed, he is in a wheelchair.

So to just say because it was family identified that we can say that's how good the benefit would look, it completely underestimates how truly valuable newborn screening would be, and I don't know if that was captured in the modeling.

DR. KEMPER: Yes. So it gives you the lower bounds of where the benefit might be.

DR. SALZMAN: Yes.

DR. KEMPER: The alternative was to say that the family identification didn't add value because of the uncertainty, in which case we wouldn't be able to do anything and have any sense of the benefit.

DR. SALZMAN: Right. You know, we're dealing with small numbers, so I just, you know, I

understand some of the limitations.

DR. KEMPER: Yes, right.

DR. SALZMAN: The other thing, it wasn't clear if you put in your numbers the heterozygotes that would have been identified. It didn't look like it based on the numbers, no.

FEMALE PARTICIPANT: They were not included.

DR. KEMPER: Those --

DR. SALZMAN: So what wasn't noted, were all of the future generations of ALD kids that are not being born because they're -- I mean if you take my case, I know I'm a carrier, I made sure that my second child did not have ALD.

I saved the healthcare system a huge amount of money because if I didn't know I was a carrier I could've had another ALD kid cost millions of dollars again.

So when people complain about not having the money, I understand it's different pockets and it's different timing to get things off the ground

in the lab, but if you just do back of the envelope calculations, you are in a saving mode overall in the pocket of healthcare very, very quickly if you just prevent a couple of ALD kids from being born.

DR. KEMPER: Yes. So we, you know, we avoid, you'll notice there are no dollar numbers in there --

DR. SALZMAN: Right.

DR. KEMPER: -- and we also, you know, for various reasons don't cost into value of the life prevented, so it's just that ---

DR. TARINI: I'll bring up two good points on the heels of that and what Carol said, and I don't remember, so I'm wondering if there is a way to pull this up or will it happen during the committee report, which is what are the actual benefits that the Committee is deciding based upon?

I know there has always been a broader discourse in the background of should the benefits be related to the child themselves or other family members?

Should the type of benefits be medical or should they be social or should they be societal? And Carol's point about benefits to other family members goes outside the child and as the reproductive benefits.

So I just want to clarify what are actually the benefits that a mandatory program like this has decided, and this Committee has decided to use as the basis for the judgment?

DR. KEMPER: Don't look at us.

CHAIRPERSON BOCCHINI: Okay. Well that was just going, that certainly, that'll come out in discussions with the presentation by the Committee members and then the discussion. Microphone?

MS. SEEGER: Yes. Can we go to the last slide with the harms listed?

DR. KEMPER: Yes. You mean the one at the very, very end?

MS. SEEGER: Yes.

DR. KEMPER: All right.

MS. SEEGER: So I'm a little confused why identifying females and other disorders would be a harm? I mean I'm looking at it as the females will now have the knowledge when they are of childbearing age.

Number two, the mothers might know so if they are having more children they can take precautions, and then, again, having a baby girl that's an ALD carrier will also allow you to identify other family members just as Marty right here, he's a perfect example of that, so I'm confused why that would be a bad thing.

DR. KEMPER: So that's an excellent question and I first of all don't mean to diminish the potential value of having that information nor do I mean to diminish the harm of being a heterozygote, because as I mentioned in the beginning the heterozygote females can develop symptoms although not until later.

And I certainly don't mean to diminish the, you know, the harm that having undetected AMN

or AMN in general can have on your life. So our charge in doing this review is to look very narrowly at the direct benefit to the screened child.

And so although there are lots of benefits that could accrue to other family members or, you know, being able to make informed reproductive decisions or being able to seek care or avoid the diagnostic odyssey either for an individual with AMN or for a heterozygote female.

Those are all real things and I don't mean to diminish any of them by listing them this way. The issue is through how the Advisory Committee views the purpose of newborn screening.

If it's solely to benefit an individual child during childhood then it's a different conversation than if you are going to look at all these other impacts.

And so I tried to best, you know, the best I can, I am glad you brought up this point, to balance all these things.

The other thing is just from a pure

evidence standpoint, you know, we can't talk about the benefit of identifying AMN in a presymptomatic individual just because those data aren't there, you know what I mean.

And it's not to diminish it like I said, absence of evidence doesn't mean that there is no benefit or harm or anything. It just means that it's just not something that we can comment on.

One of the things I anticipate seeing is a vigorous discussion once we're done with this part about really who the benefit of screening is going to be, but we were able to focus in on the population that would most likely benefit in the newborn period or the newborn into early childhood period, which would be those individuals with the childhood cerebral ALD.

Does that make sense? So it's mostly a methods question.

MS. SEEGER: No, I absolutely understand that and I understand that the boys with X-ALD are the focus. I'm just concerned that it's

labeled a harm, that's my concern because it's really not a harm.

(Simultaneous speaking)

DR. KEMPER: Right. Well there is some people that do, I mean just in terms of balance, do consider knowing, you know, carrier status, although it's not really saying that carrier status is a potential harm, or if they were to have a disease that would develop in adulthood they would rather find out at another time.

So, for example, you could screen, you know, somewhere in childhood or in adolescence, that kind of thing, to identify, you know, some of these issues earlier, so it's really just a matter of when.

And, you know, it's interesting in the Netherlands they've gone through this very same set of conversations we are having right now and they have agreed to, or they plan to adopt newborn screening for ALD, but they are only screening boys, so they are very purposely not screening females.

So there's, you know, different people come to the table with different views about harms and benefits and so to try to, you know at least from an evidentiary standpoint, just focus in on the group that's most likely to receive a direct benefit of screening in the newborn period.

But, again, I don't want anyone to walk away thinking that our group, you know, dismisses any benefit to anyone else.

MS. SEEGER: Okay. I have one more comment as well, just going back to the cost factors, and I know every State is different, but just to give you a little bit of background my son's medical bills for ten months living in the hospital were over $4 million and it cost the State of New York last year to test 250,000 babies about $500,000.

So you can see the example of just one child that was diagnosed too late and what the cost factors were associated with that.

DR. KEMPER: Yes, thanks for sharing

that, that's very helpful.

CHAIRPERSON BOCCHINI: Carol?

DR. GREENE: I appreciate the answer but I think it will be relevant to the discussion. I really would like to second the plea that you not list as a harm the identification of others.

I think it's fair to list as a harm to, you know, that it may be costly, there may be more follow up, I think it is probably fair to say that the concern about learning about adult onset diseases is more for the diseases where there is no treatment, but if it's a disease where there is a treatment and you can, you know, be monitored so that -- I mean think of, a hypothetical benefit would be the baby girl picked up as a heterozygote and she got it from her dad and he's one of the symptomatic but not diagnosed adrenal insufficient patients and then she actually gets to keep her daddy who doesn't die of adrenal crisis.

So I wonder if there is some way to say that this is in -- it's not one thing, it's not

something that you wanted to measure or to follow, but I really don't think it's a harm to the child or a harm to the family to identify the sister. So to call it a harm is a problem.

DR. KEMPER: Right. So from my worldview, you know, like if it were my kid I would feel the same way.

With that being said, there are populations of people who don't want to know and so, you know, I don't want to draw from analogy to other conditions, but there are lots of other conditions where people don't want to know and there's lots of examples where people know that they are carriers and it doesn't, for different conditions and it doesn't change their reproductive decisions.

So I'm just saying that like we can't -- that's an unknowable from my perspective and it's something that you guys are going to have to decide.

DR. GREENE: Unknowable is not necessarily a harm. I think to say that it is a harm -- so if you are looking at harms to the baby,

if you are focusing on that child, and if the harms are harms to the child then I don't think it's a harm to that baby to have his mother identified as a carrier or his sister.

DR. KEMPER: Right. I don't want to get stuck in this, but some people do consider that, so we just need to be, again, drawing from other conditions, so we just have to be fair to that.

CHAIRPERSON BOCCHINI: Okay. I want to move forward to the committee discussion, so then I'll take this last comment.

MS. SULLIVAN: Is the mike on? Yes. Hi, Susan Sullivan, The Calliope Joy Foundation. I actually had three questions related to the --

DR. KEMPER: Three, okay.

MS. SULLIVAN: -- data actually that you used.

DR. KEMPER: Okay.

MS. SULLIVAN: First, there is a lot of discussion about the availability of bone marrow in the cases of transplant, but in the actual case

studies that you looked at were there any occasions where people in the family risk group weren't able to receive treatment because of the unavailability of bone marrow?

DR. KEMPER: From the information we have, no.

MS. SULLIVAN: Okay. Because there is a lot of concern that that would happen, but it appears that that actually hasn't happened?

DR. KEMPER: Well one dataset was only people who got transplanted, so you would know about that, and then in the other smaller group there were some individuals that are enrolled in trials which they couldn't divulge anything about, so I don't know if there was anyone in that group that was unable to get a transplant and, therefore, they are going for gene therapy or that kind of thing.

So I can't really comment, but it doesn't appear that there was anyone who couldn't get a transplant.

MS. SULLIVAN: And, also, one of the

harms actually that you identify here we're just exposing the risk of transplant to an earlier age, but at the same time like I understand an earlier age you could have more complications but you also in a lot of cases are less or not as sick.

So in the data that you looked at were there any occasions in which people were identified in the family risk group but who had severe complications from the transplant?

DR. KEMPER: So, no, but, again, these are small numbers. I wish I did. You know, this is a really vital question, because if you talk to the people who do transplants they actually say that the risk in the very young children, by young I mean like under five, if you match them based on health status is lower in the younger ages and increases over time and it probably has to do with collection of like other viral infections and that kind of thing.

But, again, we had to cognizant that, you know, it's my job to balance things, that you

are just moving down the age of transplant.

MS. SULLIVAN: Okay. And my final question actually had to do with the Loes score and your data on the outcomes.

And so you took the mean of the Loes score before and after transplant in terms of the family group, family risk group, and then the clinical group.

DR. KEMPER: Yes, yes, keep going.

MS. SULLIVAN: So when you looked at those outcomes did you actually track the Loes score over time for the individuals and then look at the intervention of transplant rather than taking a mean?

DR. KEMPER: I would love -- I mean so these are medians in ranges, but I would love to have those data, but, again, basically the data that I am showing you is the full extent of the data that we could collect.

And I have to say that, again, you know, as a credit to the people working on our Condition

Review Workgroup, because in, you know, all these reviews that we have done this is the first time that we've had to go and try to get primary data because the information that we really thought was out there and that would be compelling was unavailable anywhere.

MS. SULLIVAN: All right, thank you.

MS. JEAN KELLEY: I have to speak. I can't go home without speaking. The direct benefit of newborn screening is the child will have the chance to be followed and live, period.

I think you are underestimating humanity. Look what New York did in like nine months and the results that they have, okay. If you've lived this disease and we have, my son is 20 years post transplant.

I belong to a Facebook group of 250 ALD families. They want to know. They are not playing if they are a carrier or not and want to take a chance. They want to know.

I want my daughter to be able to have a

healthy baby, okay. You have to put yourself in the position. Dr. Greene, thank you, it's not an epidemic. There are so many talented people.

I am in Connecticut. We have Yale, we have Hartford, we have Boston. People want to save lives, that's why they are a neurologist or an endocrinologist.

We passed in Connecticut twice, once our Commissioner was skeptical, reluctant, whatever, so we lost our $500,000 appropriation. So again we went at it and in July we got another appropriation and we are going to be working on this when we get home.

Please, Lord, this will be added to the RUSP because, also, New York, Connecticut, New Jersey, California, Tennessee, Illinois, and I spoke with the Public Health Director of Rhode Island last week, and they are statutory, they are regulatory. They don't need legislation.

But nothing good comes without hard work and it's where. You are always going to have a

small sample, a thin data, it's not going to change.

Give them three years they'll take more, they'll take three more years, and we're going to lose babies. My son's education, his special ed was $1 million.

By the grace of God my husband is a surgeon and we didn't have to depend on the State for his medical bills. Please, I beg you, think hard and at least let these states have a chance to implement and show other states, and it's probably going to be just as great as New York has been. I appreciate your time.

(Applause)

CHAIRPERSON BOCCHINI: Thank you. Okay, I guess we are -- I think that's finished. Fred will be, going to be on stage, but as he's coming up are there any liaisons on the phone who wish to make a comment or have a question?

(No audible response)

CHAIRPERSON BOCCHINI: Hearing none then we'll go ahead and turn this over to Dr. Lorey.

As everyone knows the two members of the Committee are assigned to serve as members of the Condition Review Workgroup for each condition.

And so they have been involved in the discussions and the presentations and have put together their summary with initial recommendation for the Committee to consider and to initiate the Committee's discussion, so I'll turn it over to Fred and Don Bailey.

MEMBER LOREY: Thank you. And for those of you who know me this is a sports jacket I am wearing. You don't get to see it very often so take a quick look. It might be another six months. Somebody's clapping back there.

I want to thank Alex our fearless leader because I couldn't even do this if it weren't for him. This was a very difficult review for a whole lot of reasons.

And I also want to thank the excellent, excellent ALD experts on the Review Panel and I want to thank my partner-in-arms here, Don, as the other

liaison.

So this is the chart you have seen and I won't spend too much time on it because you've seen it many times, but these are the things I will cover here in my very quick review.

This will be gratefully short compared to the previous presentations I promise. So, of course, one of the big things we need to know is net benefit and mortality is a big one and we've heard a lot about that in the last couple hours.

So we do believe the data do demonstrate a reduction in mortality from early intervention, from early family testing compared to treatment following clinical detection and you saw a number of charts with survivability up at the top, whether it be from transplant versus non-transplant or for family testing versus clinical symptoms, et cetera, it's, I felt, pretty striking.

And then getting into more of the specifics of those two studies Alex talked about, projected benefits at 15 years from two long-term

studies show averted number of cases of death through survival range from 17 to 64, and in the other averted deaths ranged from seven to 44 for treated patients.

And as we have heard many times, there is no firm published data on Addison's and that wasn't our job, but I did want to add we asked that question on one of our calls to the ALD experts and they all uniformly said they would like to see them earlier, that they would say there is a benefit.

And I don't know if that's the question that Dr. Greene was trying to get at earlier or not, but I just wanted to put that in there.

And you've seen this before, like almost everything else we screen for, will pick up other things. Some may be treatable, some may not be.

Very fortunate in having something we normally don't have in these reviews, which is New York State's year-and-a-half of screening which has been very successful.

So New York State reports zero false

positives after 1.5 years of screening, and that means not the first screening but the second screening, which is part of the screen, so by the time you run that longer GC-MS screening of I think it's seven-and-a-half minutes, or so, you are down to zero false positives and I believe that translates to a referral rate of something like 0.0009 percent, is that right, which is pretty low.

That's even lower than SCID referral. So the percentage of total infants referred for diagnostic work up is low and I think that's another point one of the people were trying to make.

And there was a smaller study by Dr. Moser, actually Mrs. Moser, which also reported no false positives. So that seems pretty firm, few or no false positives.

There is the risk of morbidity and mortality from the stem cell transplant as there is in even SCID, so we have to acknowledge that. But that risk is present for those who are identified clinically as well, so that's not necessarily a

negative due to early identification.

So conclusions on the net benefit, the benefits of early detection via family testing or newborn screening for children for X-ALD are fairly definitive based on two outcome studies and unpublished data.

Additional disorders will be detected, nothing new, and may benefit from early detection or may not. Female carriers may benefit from early detection if they are or become symptomatic.

However, we do know a certain portion of female carriers will be missed. We don't know whether those ones that are missed are the ones more likely to be symptomatic or not, but it is certainly a possibility of something that might become -- might be revealed in the future at some point.

I find a hard time with the Amsterdam study only testing males, personally, just a personal comment. Okay, net benefit certainty we consider to be high or moderate. So we are also looking at feasibility as we hone in on the A versus

B categories.

We believe because it's the most in use the New York State platform and protocol for screening is now established and there are other testing protocols that work just as well, so it's not just one thing that's out there.

It's a technology that most screening programs are familiar with because they are already doing tandem mass spectrometry. It may or may not require a dedicated instrument.

Somebody told me the other day they were actually running their metabolic during the day and actually using the same machine at night. Now I don't know enough about it to know if that's feasible, but my guess is the likelihood of a dedicated machine is probably high, but at least it's familiar technology.

As I said there are other multi-platform technologies and one advantage of some of those, because we already have, well, we have one LSD-approved and one approved by the Committee

waiting approval from the Secretary.

So many of these platforms can do all of the LSDs as well as ALD, so that may be a factor in the whole picture.

And this is somewhat repetitive, but there appear to be no significant issues with appropriate screening tests based on New York's data and a second test on program at Mayo Biochemical Lab.

So we feel the feasibility of screening is high. We think that's probably the strongest factor in this analysis of all things we're looking at. So that's where we see the red outline of high to moderate feasibility.

Readiness, the third factor, and this is -- I didn't want to repeat Jelili's study, but just to summarize, the survey and public health impact indicates, although most respondents feel that screening ALD could be implemented between one to three years, it is critical to recognize that to obtain funding for the screen test was seen as a

major challenge, and that varies from State to State.

California happens to be one of those three states that Jelili mentioned that has a mandate with a contingency that it can only begin after approval.

But as it turns out that's an advantage for them as it relates to the funding, because at least in California you need the legislation before you can raise the fees to increase the funding, so in this case they are a step ahead by having that law passed even with the contingency, so they are already working on it.

And as I said a number of states have legislative mandates to begin and most are already working on test development and an APHL document gives great detail on feasibility of implementation of ALD and it is mixed.

So we thought about this long and hard and we settled on A2 as the category that we think most fits the evidence.

Initially we were looking at A3 and then we realized that last statement under A3, Public Health Departments are unprepared for screening, is not the case, because at least one State is already screening, there are two or three more already starting to work on it, so we thought developmental readiness was probably a more accurate description.

So our recommendations to the Committee are that ACH(d) and (c) recommends the newborn screening for X-ALD be approved under Matrix Category A2.

Substantial work will need to be done in most states to fund, develop, and implement screening for X-ALD. States should be encouraged to implement screening within one to three years of approval for inclusion of X-ALD on the RUSP.

However, as I mentioned a couple of minutes ago, evidence from SCID indicates there will be outliers, of course. Every State faces different types of problems, many of them are logistic, many of the are political.

It's now five years after the SCID recommendation and there are still about a quarter of the states not screening, and that's not because they don't want it to, that's because they have various barriers.

And earlier doctors of newborn screening for ALD, like New York, are encouraged to obtain data in a rigorous fashion to promote continuous improvement of an evidence base regarding the risks and benefits of screening.

For the most part that simply means those first screenings start reaching demyelination stage through monitoring in New York so more outcome data can be collected.

So, I think New York has been screening a year and a half and some of the parents that presented today mentioned children affected as early as two, one, or two, or three, so I think New York will start seeing, obtaining some of these data relatively soon.

And that's all I have. I think we'll

turn it back over to the Chair.

(Applause)

CHAIRPERSON BOCCHINI: All right, thank you very much, Fred. So that's the recommendation of the members who have served on the workgroup that now is open for discussion by first members of the Committee. Dr. McDonough?

MEMBER MCDONOUGH: Steve McDonough. I thank you for your excellent work and I am fully supportive of recommending that ALD be a, A2, betterization and we encourage the Secretary to add that to the RUSP.

As a rural pediatrician's perspective, if I had any child in my practice with ALD I would want to know about it as soon as possible.

I would not want to come to the office one day on Monday and find out that one of my patient's had come to the emergency room over the weekend, had died for undiagnosed Addison's disease or adrenal insufficiency.

That is a terrible ticking time bomb out

there. So from my perspective dealing with children with rare conditions the sooner you know the better you are off and that's from my perspective, and also I'm sure the perspective of the family.

I think there is plenty of evidence that with New York's experience that the testing is feasible.

They are off to a good start, but my perspective is substantial information that there's impact on mortality and I think there will be a tremendous impact on morbidity, reducing disability, by these children being picked up sooner.

I think it's also important that we do what we can as a Committee in advice to the Secretary that if the Committee does support this as an A2 that we request that resources be provided, a program, so we don't end up with SCID, five years later with a number of states still not offering the testing, which I think pretty much universally people

believe a SCID recommendation was an excellent one and one that the Committee can be proud of.

So, again, I fully support A2 recommendation and hopefully we have a chance to make a motion whenever the Chair would entertain it.

CHAIRPERSON BOCCHINI: I think you could make that as a motion if you wish.

MEMBER MCDONOUGH: Okay. I would recommend that the Committee go on record supporting the A2 determination for ALD and then to support states with limited budgets that the Committee also encourages the Secretary to develop a comprehensive program to further assist States in meeting this recommendation.

CHAIRPERSON BOCCHINI: Thank you. There is a motion, is there a second?

MEMBER LOREY: I second.

CHAIRPERSON BOCCHINI: Dr. Lorey seconded.

MEMBER LOREY: If I am allowed.

CHAIRPERSON BOCCHINI: Definitely

allowed. All right, so is there any additional discussion? Dr. Botkin?

MEMBER BOTKIN: Jeff Botkin. Yes, I certainly very much support the analysis and thanks to you guys for excellent work on a difficult topic.

I wonder if we could put the recommendations up, because I think it wasn't just the A2. I want to take another look at what you've said there and my main concern sort of relates to what I had said previously, or a question I raised previously, which is how do we collect better data going forward here?

Because, you know, I'm sort of not comfortable with just simply saying okay, this is a positive, let's go forward, and not having adequate data collection prospectively from here on to sort of characterize two things, you know, one at a gross level is, is this working or not.

I think we have high confidence that it is going to work, but I think we also want to collect data on what are the barriers, where are the

problems, how can make sure that we're doing the best job we can with this situation, and so sort of -- yes, this is it. This is what I was looking for, yes.

So I mean it was, so one aspect is can we support data collection, you know, and I think Steve raised the question of money for implementation but might we request or think about resources out of Health and Human Services would do a better job of collecting data on the current state of affairs for these kids so that we have the historic controls so that we have better comparisons once we collect data through screening programs.

And that might resources be used in some fashion to help states with what I think we are seeing with New York was the challenges with the long term follow up.

Are there ways to incentivize better long-term data collection on kids, particularly with a condition like this where it's not, you won't

find out within six months whether you've had an impact or not, it may well take a couple of years.

So I don't have any specific recommendations in that regard but I want to think about those, the blue parts of the recommendation here.

CHAIRPERSON BOCCHINI: So in previous recommendations we have asked that the early adopter states, the data from those early adopter states be utilized to help inform how to proceed with other states and in some cases it was with the test development, but clearly it should also include outcomes for the individual patients as well.

So I think if you'd like to pose that we could easily put that in the letter to the Secretary to support that and so I think that could be proposed to add to Dr. McDonough's motion, but I think that's a really important part of this, and so I think it's appropriate.

MEMBER LOREY: Dr. Bocchini, I notice

that there is already an ALD entry on the R4S data collection. I don't know if that's appropriate, but --

CHAIRPERSON BOCCHINI: That's helpful, okay, good. So that's all --

MEMBER PARISI: Melissa Parisi, NICHD. I might point out that there is a precedent for the Newborn Screening Translational Research Network to compile data from early adopting states for conditions that have been added to the RUSP in the past number of years and that that is a potential avenue for collecting such data and going forward.

CHAIRPERSON BOCCHINI: We can easily put that in the recommendations just as a reminder. Okay. And then, Andrea?

MEMBER KELM: I guess I just wanted to raise one question, you recommended A2. I guess I didn't feel that this in terms of readiness was very different from MPS 1, which was a three.

I didn't know, you know, and I don't think a lot of states before, I don't know why this

one wouldn't be for consistency sake also be considered a three.

I didn't know if you wanted to comment on that with no states having really moved forward yet.

MEMBER LOREY: Originally we did have it as a three and the reason we changed is, and we don't have it up there, but the specific wording under three says something like not ready, and the fact that we have New York already screening, we have California, Connecticut, and New Jersey working on it, that was the reason I think for moving it to two, and the strength of the test.

MEMBER KELM: I'm also, when we are talking about funding, have we had some push back before from the Secretary in terms of seeking or requesting funding?

I just want to make sure we're not putting forth something that has not been successful although we want it. I just want to make sure that our letter is strong.

It seems like sometimes the funding questions have been pushed back.

CHAIRPERSON BOCCHINI: Yes, I think it's important the way it's worded. I think when we put forward the Pompe decision we did include a recommendation that pilot studies be done and the feedback we got was that this was, that that was in progress, that NIH was involved in developing and funding states for private studies, and so I think it's appropriate for us to continue to do that and we'll make sure it's worded appropriately.

MEMBER WILLIAMS: So this is Andrea Williams. I just wanted to say Dr. McDonough had put in his motion that in states that have limited budgets, I just think funding for state, support for State and take the limited budgets because they all will say I have a limited budget.

CHAIRPERSON BOCCHINI: Don?

MEMBER BAILEY: I just wanted to say first of all thanks to Fred for doing the presentation and integrating these data, and

especially thanks to Alex and to K.K. and the whole evidence review group.

They did go above and beyond for the condition, whatever the name of it, they did go above and beyond the call of duty here. Frankly, the data that we were looking at initially were very skimpy and, you know, Alex had to go and find new data to make a more compelling case for us.

I think we need to ask ourselves as a -- and so I'm very supportive of the nomination, but I do think we need to ask ourselves as a Committee what are some lessons learned here in terms of the future nominations and what we expect from nominators.

This disease has been studied for years. These treatments have been out there for years. Someone should have been analyzing these data and answering these questions much earlier.

It's possible to have answered them and provided them in ways that would really make our job so much easier, because it is, in reality I think

we all agree this is a good decision.

We're just bound by data that we just really need to have and so I think whatever we can do to help future nominators to provide us with the very best data to make our decision, make it an easy one and not ask, not have to go out and search for other data would be really important.

MEMBER SCOTT: Yes, I'm going to echo that because, again, I am very supportive, but if you take a very strict approach of what is A level data and what is B level data, and A level data is the data that if additional data becomes available you don't expect it to change your conclusions, whereas B level data is such that because of the small numbers, the unpublished data, et cetera, et cetera, additional data can alter your conclusions.

So I think if you took a really strict definition about the data that's been presented and then it's available to us, it's really B level data.

Again, I am supportive, but just because of the quality and the quantity of the data.

MEMBER THOMPSON: I would echo Joan's point, it also raises the question that, you know, we spent a considerable amount of time a few years ago creating this construct to be able to facilitate our ability to give guidance to community organizations or disease-specific organizations as well as to the Committee itself in its deliberations and I find it very challenging to think that this is the second highest level and the quality of data that we are being at.

I personally don't believe that that's the case. I think that this is at best B level data just as you are suggesting and it does not mean that, at least from my point of view, I am not unsupportive of the effort, but I think that if we are looking at trying to judge this condition and future conditions we are setting this bar remarkably high on really very little data.

DR. TANKSLEY: Susan Tanksley, APHL. I just wanted to comment in regard to Kellie's comment earlier about a State's readiness to screen

and just to remind everybody with MPS 1 there were already two states that had some degree of screening for MPS 1 when we did the vote on that as well.

DR. TARINI: Beth Tarini, AAP. I think the point about data is important, the need for more. I have two comments about the discussions about the data.

One, as the Committee already knows, the data, although incomplete, still has to meet the level as they see as you all see fit to implement mandatory screening.

So by that standard it seems that the implication is if voted upon the data that exists signifies enough data on which to base a mandatory public Newborn Screening Program.

If so, and it asked for additional data is simply to fill the uncertainties Joan points out, that this data may be a point estimate that has some movement to it then in collecting additional data, even though we have the ability to do so through existing networks, we do not have in place a

mechanism to review it.

Not that I want to give Alex more work, but we can't -- I don't see how in good conscious we can say we performed an evidence review on the front end, don't get as much as we would like, collect the data on the back end, and then don't have a system to review it by the same rigorous standards.

So I just wanted to put that thought out there.

DR. MCCABE: Ed McCabe, March of Dimes. I certainly agree with the discussion about the need for more data. However, I want to place the illness where the illness is.

It wasn't the families that were sitting on this data. It was the investigators that were sitting on this data.

Now I think if we say that we have to have adequate data before we bring -- before someone nominates this, then we're putting the onus on advocates and I really think we ought to put the onus

on the investigators who are sitting there and, you know, I mean I have papers I haven't published, and so I understand the competition for our time, but I don't think we can hold the nominators to that standard.

MEMBER WICKLUND: Yes, I just want to second that, too. This is Cathy Wicklund. I think my biggest concern out of all of this is like you said, you know, lessons learned, is really there is data there but no one is publishing it.

And we all know, I agree, we're, you know, you're busy and you are trying to get things done, but I think that's the part that is just, to me, a really big deal in this is that why isn't it getting out there in some form or the other?

You know, is there another way that it can get out there, does it have to be in a published peer review journal, I don't know, but I think that's a big issue that we are dealing with right now.

MS. MOSER: Okay. I wanted to give my

thanks to the Committee for their hard work. Listening to all the conversations about the data, there is an organization called ALD Connect and one of their mandates is to gather more data on ALD.

And going forward I think that the family organizations will make it a priority to get the data needed for study of the efficacy of ALD newborn screening.

And then I wanted to say that in the last two months I have been working on a method, LC-MS/MS method, because I am doing high throughput screening for drugs to treat ALD and I have developed a 2-minute assay. Using the CDC standards it can be done on an AB SCIEX 3200 in two minutes, very low cost.

So I will publish this method and the states can use that if they want to set up a standalone test for ALD. I think it might be very useful.

(Applause)

DR. GREENE: With the focus on the ALD

and all the important issues about data collection that go beyond ALD in the systems and one question is do you hold ALD to a different standard than previous discussions because there is still not a data system, so you want to solve the data system, but I hope that can be separate from the discussion of ALD.

And coming back to the question of B versus A, that's going to be a really important discussion for the members of the Committee. I would suggest as a personal interpretation that even though there is very, very, very thin data all the data is going in the same direction and none of it overlaps zero.

So I think that going by the language there is a high certainty of significant benefit. It's not clear how much benefit, but I think for me the B means we're really not sure that it's, we're not completely 100 percent sure that it's a good thing to screen.

It's not that -- I mean it seems to me

that there is solid data, we're not sure how much exactly, but there is a very, very big difference between the lives saved and even a bigger difference between the lives saved walking and talking that it doesn't come even close to zero, it's not in that range.

So for me it's still an A just because of the big difference and everything is going the same direction, but it's for the Committee to decide.

CHAIRPERSON BOCCHINI: All right. If there are no other comments, currently the motion to recommend the inclusion of ALD in the RUSP with an A2 recommendation with the caveat as included by Dr. McDonough of asking the Secretary to help provide additional support and then to use data from earlier adopting states to provide additional information concerning ALD and whatever else is found based on this recommendation. So --

MEMBER SCOTT: Just to make sure that the recommendation for the data includes everyone

who is identified, including, you know, the girls and, obviously, the mothers who are going to be heterozygote carriers, so we want to capture the full phenotypic in everybody not just what happens to --

CHAIRPERSON BOCCHINI: Good point, Joan, thank you. Okay, all right. So with that we are going to go around the table and vote. I'm going to start alphabetically with Don Bailey.

MEMBER BAILEY: I vote to approve or agree or yes, or whatever.

CHAIRPERSON BOCCHINI: A vote to approve. Dr. Botkin?

MEMBER BOTKIN: Approve.

CHAIRPERSON BOCCHINI: Coleen Boyle?

MEMBER BOYLE: I vote to approve.

CHAIRPERSON BOCCHINI: Melissa Parisi?

MEMBER PARISI: Approve.

CHAIRPERSON BOCCHINI: Kellie Kelm?

MEMBER KELM: Approve, although I prefer A3, but I think we're giving support to the

states to hopefully move it up.

CHAIRPERSON BOCCHINI: Okay, thank you. Fred Lorey?

MEMBER LOREY: Approve.

CHAIRPERSON BOCCHINI: Dietrich Matern?

MEMBER MATERN: I recuse myself from voting as I did from the discussion because of a potential conflict of interest that people might see some time in the future.

CHAIRPERSON BOCCHINI: Thank you. Steve McDonough?

MEMBER MCDONOUGH: Approve.

CHAIRPERSON BOCCHINI: Kamila Mistry?

MEMBER MISTRY: Approve.

CHAIRPERSON BOCCHINI: Joan Scott?

MEMBER SCOTT: Approve.

CHAIRPERSON BOCCHINI: Alexis Thompson?

MEMBER THOMPSON: I vote no.

CHAIRPERSON BOCCHINI: Cathy Wicklund?

MEMBER WICKLUND: Approve.

CHAIRPERSON BOCCHINI: And Andrea Williams?

MEMBER WILLIAMS: Approve.

CHAIRPERSON BOCCHINI: So the motion passes and we will get a letter to the Secretary as soon as possible.

(Applause)

CHAIRPERSON BOCCHINI: So I would like to first thank the Condition Review Workgroup. I think I agree this has been an outstanding job.

Alex Kemper, I want to thank him specifically, and K.K. Lam, who was the project manager for this project, and I agree with Don's comment that there was a remarkable amount of additional work that was done to help identify some of the critical information to help this Committee make this decision.

So I certainly want to thank them. I want to thank Lisa Prosser and Jelili as well for their contributions to the evidence review. I

think those were incredibly helpful as well to make this happen.

But I really want to especially thank the parents, the families, and the persons affected by ALD for their taking the time and making the effort to come here on a regular basis to help us understand the impact of this on families and help us in our deliberations, so I want to thank you all for your participation. Thank you very much.

(Applause)

CHAIRPERSON BOCCHINI: Okay. So, unfortunately, we are going to be timed out from the webinar so we got to make a quick summary of information for the workgroups as to where they are going to meet and how they are going to meet and we'll have to do that very quickly and then we'll close out.

MS. SARKAR: Okay. So the members of the various workgroups you should've gotten an email about meeting today. The Timeliness Workgroup you will stay here in this room.

The Cost Analysis and the Pilot Study Workgroups, if you could all meet by the cafe outdoors, we need to escort you across the street to the Parklawn Building where there are two meeting rooms over there.

I think maybe we can take a 10-minute break after Dr. Bocchini has adjourned the meeting and then at 4:10 we will walk over. Thank you.

CHAIRPERSON BOCCHINI: Okay. We have time for one last comment at the microphone.

MR. MORRIS: Thank you, Dr. Bocchini. My name is William Morris. I am the father of two children with recessive disorders, Krabbe's, my son Grayson passed away from that, and my son Seth has PKU.

I just wanted to address the issue that was mentioned several times about the feasibility for states to implement recommendations to the RUSP and I wanted to encourage the family members that their motion is very powerful and please educate your family and friends about newborn screening and

there are multiple foundations that have avenues to get supplemental newborn screening that will fill the gap until the states are able to come up to the RUSP.

So there are ways to receive Pompe screening, SCID screening, the MPS 1, and I'm sure ALD will be soon to follow. Thank you.

CHAIRPERSON BOCCHINI: Thank you very much. So with that we'll conclude today's meeting. I want to thank especially the Committee members and the two Committee members who served on the ALD Evidence Review and I think this was a good day and a very productive day for the Committee.

So enjoy the workgroups and we'll see you in the morning. Thank you all.

(Whereupon, the above-entitled matter went off the record at 4:01 p.m.)