28TH MEETING OF THE SECRETARY'S ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

Thursday, September 13, 2012

MORNING SESSION

8:30 a.m. - 12:15 p.m.

Humphrey Building

HHS Headquarters, Room 800

200 Independence Avenue, S.W.

Washington, D.C.

APPEARANCES

COMMITTEE MEMBERS:

JOSEPH A. BOCCHINI, JR., M.D.

JEFFREY BOTKIN, M.D., M.P.H.

CHARLES HOMER, M.D., M.P.H.

FRED LOREY, PH.D.

DIETRICH MATERN, PH.D.

STEPHEN MCDONOUGH, M.D.

ALEXIS THOMPSON, M.D.

CATHERINE A.L. WICKLUND, M.S., C.G.C.

EX-OFFICIO MEMBERS:

COLEEN BOYLE, PH.D., M.S.

CHRIS DEGRAW, M.D., M.P.H.

ALAN E. GUTTMACHER, M.D.

KELLIE B. KELM, PH.D.

MELISSA PARISI, M.D., PH.D.

KISHENA WADHWANI, Ph.D., M.P.H.

DESIGNATED FEDERAL OFFICIAL:

SARA COPELAND, M.D.

APPEARANCES (Continued)

ORGANIZATION REPRESENTATIVES:

NATASHA F. BONHOMME

FREDERICK M. CHEN, M.D., M.P.H., F.A.A.F.P.

JANE P. GETCHELL, DR.P.H., M.T. (ASCP)

CAROL GREENE, M.D.

BENNETT LAVENSTEIN, M.D.

NANCY ROSE, M.D.

JOE LEIGH SIMPSON, M.D.

BETH TARINI, M.D., M.S., F.A.A.P.

MICHAEL S. WATSON, PH.D., F.A.C.M.G.

MARY J.H. WILLIS, M.D., PH.D.

C O N T E N T S

C O N T E N T S (Continued)

P R O C E E D I N G S

CHAIRMAN BOCCHINI: All right. Let's go ahead and get the meeting started. If everyone will take their seats?

(Pause.)

CHAIRMAN BOCCHINI: All right. I'd like to go ahead and get the meeting started. If everyone can take their seats, we'll go ahead and get the meeting started.

All right. If everyone will take their seats, we'll go ahead and get the meeting started.

Thank you.

I'd like to welcome everyone to the 28th meeting of the Secretary's Advisory Committee on Heritable Disorders in Newborns and Children. I want to thank you all for coming to this meeting. We're going to start off with some housekeeping notes and lunch options.

Sara?

DR. COPELAND: And I have to read them. Okay.

When exiting the general session, the

restrooms are down at the end of the hallway. Altarum staff will be at the registration desk in the lobby to direct and assist attendees and answer any questions.

If you are not a Federal employee, you must be escorted to and from meeting rooms by a Federal employee. It says HRSA staff here, but I'm going to say any Federal employee can do it.

Please note we are not able to provide wireless access in the meeting rooms.

Subcommittees, this is going to be fun, you guys. We've got two rooms, and we're sharing. Oh, no. Apparently, we have a third one. Never mind.

Subcommittees, 2:45 p.m. to 5:00 p.m. Lab will be on 305A on the third floor. Follow-Up and Treatment will be in here. Education and Training will be in 425A on the fourth floor.

If any of the presenters have changed their presentations, please save the revised copy with our gentleman at the table back there.

Lunch options, oh, so varied and wonderful

around here, let me tell you. There's a Humphrey café here in the building. It's on this level. So that's nice. At least you guys won't have to -- there's no excuse for being late to the committee members at lunch time.

There is -- oh, you guys are going to love this. There is a Quiznos down at 400 C Street. There's Potbelly Sandwiches at 400, as is the Wishbone, which is sandwiches and soup. Café Phillips, Mitsitam Café, which is, oh, across the street at the American Indian Museum, which -- but you can't be late, Advisory Committee members.

There's the atrium café on 4th Street as well, and there's a food court at the Capitol Gallery, and there's the L'Enfant Plaza food trucks for the adventurous.

So those are your housekeeping notes. Most important is just keep in mind that you need to be escorted by a Federal employee.

CHAIRMAN BOCCHINI: And then one other note for those of you around the table with microphones, that you should keep the microphone off

and only turn it on when you're going to speak. And when you're going to make a comment, please go ahead and state your name or at least raise your hand so that the court reporter -- the recorder can go ahead and indicate who made the comment.

The next item on the agenda is approval of minutes from the May 2012 meeting. Committee members have received those in their packet. Are there any additions or corrections to be made to the minutes?

(No response.)

CHAIRMAN BOCCHINI: Hearing none, I'd go ahead and ask for a motion to accept the minutes as written. Anyone?

Chris?

DR. DEGRAW: So moved.

CHAIRMAN BOCCHINI: Okay. Chris DeGraw.

Second?

DR. BOYLE: Second.

CHAIRMAN BOCCHINI: Coleen? All in favor -- oh, we need to go around first? We're going to do it by --

DR. COPELAND: Go around by name, and we can record your vote.

CHAIRMAN BOCCHINI: Okay. So we'll start with Jeff and then go around the table.

DR. BOTKIN: I abstain.

CHAIRMAN BOCCHINI: Charles?

DR. HOMER: Approve.

DR. LOREY: Aye.

DR. DEGRAW: Aye.

DR. MATERN: Aye.

DR. KELM: Aye.

DR. PARISI: Abstain.

MS. WICKLUND: Abstain.

DR. BOYLE: Approve.

DR. WADHWANI: Abstain.

DR. THOMPSON: Approve.

DR. MCDONOUGH: Aye.

CHAIRMAN BOCCHINI: I approve as well. Fred, did you get a chance to vote?

DR. LOREY: Aye.

CHAIRMAN BOCCHINI: Okay. All right. So the minutes are approved as distributed.

I have one other item under administrative business. We did receive a letter from the Secretary in response to our letter to her regarding recommendations to link the newborn screening vial number to the birth certificate so that data can be found later.

The Secretary has responded that she's referred our recommendation to the interagency coordinating committee for their review and input and expects -- she expects the committee to report by March of 2013. So that's in process.

In addition, you have -- I guess that is the only correspondence that we have received since the last meeting. So, from there, we're going to go ahead and do the roll call.

DR. COPELAND: Go ahead. I don't have the listing.

CHAIRMAN BOCCHINI: Roll call, if everyone will answer "present." We know that Don Bailey is not here, and Andrea Williams is not here as well.

So Bocchini? Yes, here.

Jeff Botkin?

DR. BOTKIN: Here.

CHAIRMAN BOCCHINI: Coleen Boyle?

DR. BOYLE: Present.

CHAIRMAN BOCCHINI: Sara Copeland?

DR. COPELAND: Present.

CHAIRMAN BOCCHINI: Kishena Wadhwani?

DR. WADHWANI: Here.

CHAIRMAN BOCCHINI: Melissa Parisi?

DR. PARISI: Here.

CHAIRMAN BOCCHINI: Charles Homer?

DR. HOMER: Here.

CHAIRMAN BOCCHINI: Kellie Kelm?

DR. KELM: Here.

CHAIRMAN BOCCHINI: Fred Lorey?

DR. LOREY: Here.

CHAIRMAN BOCCHINI: Chris DeGraw?

DR. DEGRAW: Here.

CHAIRMAN BOCCHINI: Steve McDonough?

DR. MCDONOUGH: Present.

CHAIRMAN BOCCHINI: Dieter Matern?

DR. MATERN: Here.

CHAIRMAN BOCCHINI: Alexis Thompson?

(No response.)

CHAIRMAN BOCCHINI: No. And Cathy Wicklund?

MS. WICKLUND: Present.

CHAIRMAN BOCCHINI: Okay. And then we go down the organizations?

DR. COPELAND: No.

CHAIRMAN BOCCHINI: Okay. Thank you.

So the first item up for presentation today is an update -- related to update on RUSP conditions, and first, we'll have an update on newborn screening case definitions by Jelili Ojodu.

Is Jelili here?

(No response.)

CHAIRMAN BOCCHINI: Okay. I guess have we heard from him? Jelili?

DR. COPELAND: Here's not here yet. So --

CHAIRMAN BOCCHINI: Okay. All right.

So we can go to public comment if the presenters are here, and then when Jelili gets here, we'll go for the RUSP condition presentation.

So we have four individuals who have

signed up for public comment. Based on the schedule, we've divided their presentations into 2-minute presentations each.

And if they can come forward to the microphone to make their presentation? First on the list is Dean Suhr.

MR. SUHR: Good morning. Thank you for the opportunity to speak before you.

I'm Dean Suhr. I'm the president and co-founder of the MLD Foundation. I also wear another hat as the advisory board for the RARE Project out on the west coast.

But today I'm speaking with you on behalf of the MLD Foundation and the families with metachromatic leukodystrophy. MDL is related to ALD and to Pompe, two diseases you'll be talking specifically about here. We're not here to request for newborn screening just yet, but we do appreciate the work that goes into this process.

The challenge with MLD is a pseudo deficiency. So our diagnostic screening would throw out about 1 in 12 of those children that are tested,

and obviously, that's not manageable at this point. But we'll keep working with the scientists and make progress on that. And we have therapies, a couple in clinical trial and one coming into clinical trial next year.

But I'm not here to talk to you specifically about that. I wanted to broach another topic, which is that of a change in sentiment that is occurring with a lot of the rare disease foundations and is also being driven and, of course, is being driven by the families as well. And that's in the area of newborn screening where there is no viable therapy.

We're a strong supporter of the process. We're a strong supporter of this committee and the mechanics that you've put together to review all of the potential candidates for screening. And we recognize that having a viable therapy is one of those criteria.

But I just wanted to make you aware that the sentiments that are changing with regard to not having therapies are related to things like quality

of life, accessing services if you know you have a disease, avoiding diagnostic odyssey, being able to maybe accelerate the gathering of data in patient communities that would be necessary -- or identification, excuse me, of patient communities that would be necessary to do some of the science that's necessary to get to the diagnostics and the therapies and so on.

So it's a very complicated issue. We certainly don't underestimate that, and I just wanted to make myself personally available as well as just report on that sentiment change to start looking at and considering changing the policy related to that particular criteria.

So thank you.

CHAIRMAN BOCCHINI: Thank you for your comments.

Next is William Morris.

MR. MORRIS: Good morning. Thank you for the opportunity to say good morning this morning.

I'm with the Grey's Gift Memorial Foundation down in Texas, and I just wanted to again

mention to the committee that we appreciate all your hard work and encourage for a statement from this committee in regards to getting the secondary panel up and running nationwide by 2015.

I think that that is something that we really need to push forward and try and get the States to comply. Several of them have still not gotten their full secondary panel up and running.

Thank you.

CHAIRMAN BOCCHINI: Thank you.

Next we have Sarah Wilkerson.

MS. WILKERSON: Good morning. Hello, my name is Sarah Wilkerson. And I'm a parent, and I'm also an advocate for the Save Babies through Screening Foundation. And I wanted to talk to you today about my son Noah.

Noah lived for 4 precious days in June of 2009 before he suddenly and unexpectedly stopped breathing and passed away. We discovered afterward that he had a genetic disorder called MCAD, which is an illness that's 90 percent treatable if we had the diagnosis in time. But unfortunately, Noah's

diagnosis came too late for us to be able to do anything about it.

My husband and I live in the State of Colorado. We moved there just before Noah was born but are originally from the State of Missouri. And upon further investigation, we learned that the services offered between the two States differ drastically.

In the State of Missouri, they have four State labs that run continuously. They have policies that dictate when the initial blood sample is collected, how the samples are shipped to the State lab, and how long the State lab has to process the results afterwards. And as a result, they haven't lost a child to a disorder like Noah's since 2004.

In our new home State of Colorado, they didn't have policies in place that were as aggressive. They use the U.S. Postal Service to mail samples in, and they'll wait to batch samples until they can warrant sending a package big enough to the State lab.

The State lab is closed on evenings, weekends, and holidays. So depending on the day of the week your baby is born, you could be in for a bit of a wait.

So today I'm here today to talk to you about this and the fact that if we had never moved, odds are my son would still be alive today. What I would like to request is that you guys make a recommendation that hospitals collect the initial blood sample at 24 hours of life, that you no longer condone the use of the U.S. Postal Service to mail samples to the appropriate State lab, and to hopefully recommend that the State lab would process results within 48 hours of receiving it.

It's vitally important that these recommended procedures be put into place and that the Secretary of Health and Human Services adopts them. Because in cases of infants like my son, days, minutes, and seconds matter the longer that it takes a genetic diagnosis to come through.

In the end, parents like me deserve to know as soon as is humanly possible that their child

has a life-threatening illness so that they have options, which are options that I didn't have, which was to fight for my son's life.

Thank you for your consideration.

CHAIRMAN BOCCHINI: Thank you for your comments, Ms. Wilkerson.

Next we have Christine McCormick.

MS. WILKERSON: Christine was unable to make it today. So she gave me her comments to read instead.

Dr. Bocchini and ladies and gentlemen of the committee, thank you for allowing me a moment to speak to you today. I'm speaking on behalf of the Save Babies through Screening Foundation.

Our president, Jill Levy-Fisch, could not be here today, and therefore, I'm reading comments on her behalf. It is exciting to address the committee during Newborn Screening Awareness Month, the very awareness month started by our organization many years ago.

Since 1998, Save Babies continues to be the only national nonprofit organization in the

country solely dedicated to the advocacy of newborn screening. We are all volunteers who have been personally touched by newborn screening.

Our Web site is a valuable resource for the public, and in addition, we engage with families on all levels. We are readily accessible via email, and our toll-free number is manned by experienced newborn screening advocates at all times.

In honor of Newborn Screening Awareness Month, we created a toolkit that was pushed out via social media and email by the National Library of Medicine, the National Healthy Mothers, Healthy Babies Coalition, several State Departments of Health, and many other groups.

We are also issued a significant grant by the Partners of the Heart, which will help us achieve our mission and goals. We are currently wrapping up production of an educational video regarding blood spot retention and privacy issues.

The 50th anniversary of newborn screening is a wonderful milestone to celebrate. We'd like to make you aware of our current resources and plans to

facilitate programs, such as Newborn Screening Recognition Day in States across the nation.

We believe that parents and children are the heart of newborn screening and have many advocates ready to share their stories and experiences with you. For over 14 years, we have been a passionate and dedicated voice for babies and will continue to be this, as this is who we are.

Our robust marketing and outreach channels through social media, traditional media, and email lists, combined with our personal experience, sets us apart in a way that cannot be matched. We'd like to leave no stone unturned, and on the 50th anniversary of newborn screening are here to be a collaborative partner with your organizations.

Newborn screening would not be where it is today had it not been for the tireless work of advocates in conjunction with the dedicated public health professionals.

Thank you.

CHAIRMAN BOCCHINI: Thank you. And you can tell Ms. McCormick that her comments were read

quite well. Thank you.

(Laughter.)

CHAIRMAN BOCCHINI: Next we have the presentation of the ALD group, a series of comments from the ALD group.

DR. RAYMOND: Good morning. I'd like to thank -- my name is Dr. Gerald Raymond.

Good morning. I'd like to thank the committee for allowing us to speak this morning.

I'm the Clinical Director of Neurogenetics at the Kennedy Krieger Institute in Johns Hopkins Hospital. I'm here today as a clinician and researcher in the field of X-linked adrenoleukodystrophy, and I'll do brief oral comments about what we know about ALD and why it's important to do newborn screening.

I wish to emphasize a few points. Since the initiation of plasma very long chain fatty acid testing over 30 years ago, we have learned quite a bit about X-ALD. We understand the genetic and biochemical abnormality present in all tissue of the body, and it's diagnosable at birth. Has an

incidence of about 1 in 17,000.

In all, I think -- and we understand the natural history of this disorder. It predominantly affects the adrenal glands and the nervous system.

Primary adrenal insufficiency, or Addison's disease, occurs in the majority of affected males. In some, there is evidence of an elevated ACTH, which is the hallmark of primary adrenal insufficiency as young as 5 to 6 months of age.

Adrenal insufficiency is a major cause of morbidity and mortality and often goes unrecognized with tragic results. I'm personally aware of a 26-month-old child who died of an adrenal crisis who was only diagnosed after his death.

The other aspect is the neurological presentation, the childhood cerebral form of the condition, which affects approximately 35 percent of at-risk boys. The only therapy for this is bone marrow transplant, and it's highly effective in boys who are at risk and prospectively monitored with MRI.

Clearly, for both manifestations, this is an opportunity to intervene in an asymptomatic period. But attempts to capture this population have been very limited.

After consultation with those in the newborn screening field, it was proposed to explore this avenue. We developed the method. Using the standard blood card and tandem mass spec, we have determined that it is accurate and robust and have piloted it in Maryland. We are presently offering it as a clinical diagnostic test.

We are here today to, hopefully, move this forward to the uniform panel and improve the care of affected children by detection, monitoring, and treatment of X-ALD.

Thank you.

CHAIRMAN BOCCHINI: Thank you, Dr. Raymond.

Are there --

DR. RAYMOND: There's others.

MS. KANE: My name is Taylor Kane. I am 14 years old.

When I was 3, my dad, Jack Kane, learned that he had ALD, what was destroying the myelin in his brain. Over the next 2 1/2 years, he gradually lost the ability to walk, talk, swallow, and understand what was going on around him.

It was hard to watch because my dad was such a great father, and he wanted to live more than anything. But he passed away before he got to see me graduate kindergarten. That was the saddest day of my life. My dad will always be my hero.

My dad wasn't the only person in my family affected by ALD. His identical twin brother, Jimmy, died from ALD about a year after my dad did. I also had a cousin, Chuckie, who I never met because he died when he was 23 before I was born.

No one knew anything was wrong with Chuckie. One day, he broke his collar bone, and a few days later, my Aunt Patty found him dead. His death certificate said he died from adrenal insufficiency. No one knew he actually had ALD until years later after my dad was diagnosed.

This brings me to the first reason I think

newborns should be screened for ALD. If my cousin Chuckie had known he had the defective ALD gene when he was born, he would have been prescribed hydrocortisone for his adrenal insufficiency. A simple pill would have saved his life.

No boy should have to die like my cousin Chuckie when there is a screening test that can easily prevent it.

The second reason I think newborns should be screened for ALD is that the test can identify more than three-fourths of female carriers of the disease. Since my dad had ALD, I know I am a carrier. My mom began explaining to me what it meant to be a carrier in bits and pieces when she thought I was old enough to understand.

When I was 12, she took me to the Kennedy Krieger Institute to meet with Dr. Raymond and the genetic counselor. I understand that because I am a carrier, there is a good chance I will develop physical symptoms when I get older, such as numbness in my legs, difficulty walking, and bladder problems.

I'm glad I know this now so that I can take care of myself and get plenty of exercise to stay strong and healthy. But even more importantly, I understand that when I get older, if I were to have children, there is a 50 percent chance that each of my children would inherit the ALD gene from me.

But when I went to the genetic counselor, I learned that this doesn't have to happen. There are medical procedures that can be done before I have children so that they are not born with the ALD gene, or I could adopt. But trust me, I am so happy I know I am a carrier so I will have this choice.

Most women don't know they're carriers. They unknowingly pass the ALD gene to their babies. No woman should have to find out that she is a carrier by having a baby who gets sick or dies from ALD. All newborn babies, boys and girls, should be screened for ALD.

Thank you.

CHAIRMAN BOCCHINI: The committee thanks you for your comments. Appreciate it.

MR. BARSH: Hi. My name is Spencer Barsh, and I am here on behalf of the ALD Foundation.

After many years of misdiagnosis, my cousin Oliver was diagnosed with adrenoleukodystrophy, ALD. I was 1 year old when this occurred. This led to me being tested and learning that I, too, was born with ALD and had a time bomb ticking inside of me counting down how long I would get to live.

When I was 2 years old, I had a cord blood transplants and stopped the time bomb from going off. Now I am a happy and healthy 12-year-old.

I am here today to urge you to approve newborn screening for ALD. If newborn screening was available at the time my cousin Oliver was born, he would be alive today. Instead, his time bomb went off before it could be stopped.

It took years of going to doctors to find out what was going on, and by then, it was too late to help him, since transplants do not work at that stage of the disease.

When my mom learned that she was a carrier

of ALD, she made sure that she had a healthy little -- oh, sorry. She made sure that I had a healthy little sister who doesn't have ALD.

Oliver died at the age of 12 years old, a few years after he was diagnosed. I'm alive and healthy because Oliver was the ALD screen for our family. 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 be saved as I was.

Thank you for your time.

CHAIRMAN BOCCHINI: Thank you.

DR. MOSER: Good morning. My name is Ann Moser. I'm a research associate at the Kennedy Krieger Institute in Johns Hopkins Hospital.

My late husband, Dr. Hugo Moser, and I developed an interest in studying ALD in 1978 when the group at Albert Einstein reported that patients with ALD had increased very long chain fatty acids, mainly of 26 carbons chain length in brain and adrenal cholesterol esters.

In the early '80s, Hugo's research team at the Kennedy Institute developed gas chromatographic assays of the very long chain fatty acids, first in cultured cells and later in plasma, and we diagnosed patients with ALD. After the plasma C26.0 assay became available, many families with ALD were identified, and therapy trials began.

One of the most important and available life-saving therapies for ALD is hormone replacement for those ALD patients with Addison's disease. Dietary therapies with oleic acid and later erucic acid, Lorenzo's oil, were shown to lower the plasma very long chain fatty acids. And those young ALD boys identified through family screening whose plasma C26.0 levels were normalized were 75 percent less likely to develop brain disease by the age of 10 years. However, those ALD patients who started Lorenzo's oil therapy after the brain disease did not benefit from dietary therapy.

Since the early 1990s, bone marrow transplantation was shown to be effective in halting the central nervous system demyelination if done at

the first signs of progressive brain dysfunction. By 2010, several hundred ALD boys have benefited from bone marrow and umbilical cord cell transplantation.

It was Hugo's dream to identify boys with ALD early, at a time before Addison's and brain dysfunction occurred. In 2005, Hugo suggested to this committee that ALD be added to the list of disorders that would possibly benefit from newborn screening. However, at that time there was no test for ALD utilizing the sample collected on all newborns, the heel stick blood spot.

In order to develop a newborn test for ALD, Hugo and I contacted Walter Hubbard at the Department of Clinical Pharmacology at Johns Hopkins. Walter is an expert in liquid chromatography tandem mass spectroscopy of lipids, and he was interested in helping us devise a test for ALD using the newborn blood spot.

We first used LC/MS/MS to measure the C26.0 fatty acid content of the dried blood spot and also the C26.0 content of other lipids, such as

ceramides and sphingomyelins, but found that naturally high red cell C26.0 content interfered and gave many false positives.

Finally, in January of 2006, we determined that the C26.0 content of the lysophosphatidylcholines was 5- to 10-fold higher in the venous blood spots from ALD patients when compared with controls. This finding was published in the Molecular Genetics and Metabolism in 2006.

There was still much more work to be done to validate the assay. We contacted Walter Shaw at Avanti Lipids and paid for the custom synthesis of an authentic C26.0 lyso PC standard and a 4 deuterium labeled C26.0 lyso PC as an internal standard.

With IRB permission, we obtained the newborn blood spots from known ALD patients born in the States of California and Michigan. At the same time, we also tested anonymous leftover newborn blood spots from the States of Maryland, California, CDC, and Costa Rica, found no positives.

The ALD newborn blood spot had 5- to 15-

fold increased C26.0 lyso PC with no overlap when compared with the anonymous newborn blood spots. These findings were published in 2009. Since that time, we have developed a high throughput LC/MS/MS screening procedure and have published a combined extraction of the C26.0 lyso PC with that of the acylcarnitines.

Recently, together with the Maryland State Newborn Screening Lab, we have completed the screening of 5,000 consented newborns born in 3 local Baltimore hospitals, and we did not find one positive. Thus, we believe that using our procedure has a low false positive rate.

Hugo Moser died in 2007 knowing that his dream of ALD newborn screening was possible. We are here today on the behalf of all ALD researchers, the ALD support groups who have donated funds to ALD newborn screening, and many ALD families worldwide to request that ALD be added to the uniform panel of screening tests performed on all newborns.

Thank you for your time and consideration of this important life-saving request.

CHAIRMAN BOCCHINI: Thank you, Dr. Moser. And certainly the committee wants to recognize all the contributions made by you and your husband in the development of our understanding of this disease and educating us about its presentation and its treatments.

If there are no additional comments from the ALD group? Okay, thank you.

We're now going to ask Jelili to come forward to give us two presentations on the update on RUSP conditions.

Jelili Ojodu is the Director of Newborn Screening and Genetics Program at the Association of Public Health Laboratories, and he is also the project director for the Newborn Screening Technical Assistance and Evaluation Program. He is responsible for providing guidance and direction for the Newborn Screening and Genetics in Public Health Program.

Prior to joining APHL, he spent 4 years at Georgetown University Medical Center on a National Institutes of Health initiative to reduce infant

mortality in the District of Columbia as a research associate. He received his Master's in Public Health from the George Washington University and a Bachelor of Science degree in Biologic Sciences from the University of Maryland-College Park.

Welcome, Jelili.

MR. OJODU: Thank you.

And good morning, everyone. My task this morning is to briefly update you all on the activities that a number of folks have been working on as it relates to newborn screening quality indicators and most especially case definitions.

I'm going to speak briefly here at the top of my presentation -- and Dr. Bocchini, thank you so much for allowing me to give this presentation here. The whole idea of collecting quality indicators and case definitions at the end of the day will feed into a newly funded HRSA cooperative agreement, NewSTEPs. NewSTEPs stands for Newborn Screening Technical Assistance and Evaluation Programs, and some of the objectives is listed on this slide here.

We're going to be providing a

comprehensive resource center to all of the State newborn screening programs. We're going to be providing technical assistance. We're developing a new database and a Web site, using quality indicators to provide pertinent information to State public health labs across the country.

So our primary audience for this particular task here is the newborn screening programs. And of course, as always, there are many other stakeholders.

I'll get back to the whole idea of NewSTEPs and how this feeds into the two presentations that I'm going to give today.

In 2004, as most of you recall, ACMG and HRSA came out with the Recommended Uniform Screening Panel, the list of conditions that included 29 core conditions and 25 secondary conditions. As part of that recommendation, there were also other recommendations to try and figure out how we can better harmonize case definitions across the country.

For the most parts, States actually define

and classify their different conditions, you know, internally, whether it's through their medical director or specialists from the States. And so, the problem has been that there has been inconsistency among the case definitions calling for cases. And when you're talking about surveillances, it's very hard to compare from case to case, from State to State the different cases. I mean, that sometimes they are different.

So comes the rationale, of course, and this goes further down the line of diagnosis, these are not often comparable. For the most part, they are, but sometimes they are not.

Oh, I'm sorry. It's not -- oh, I thought they were moving. Sorry. Thank you.

Oh, I'm just looking at them here and thinking. All right. Sorry about that.

So this is the good stuff that I talked about, about NewSTEPs, which I thought you were looking at. So sorry.

Rationale. All right. So HRSA, and I'll get to this in a minute, in collaboration with a

number of folks in this room and across States, developed a single objective in trying to figure out the best way to harmonize case definitions and nominal categories of the disease diagnosis across State newborn screening programs. And this model will be used to harmonize systems and programs and pretty much activities related to newborn screening across the board there.

HRSA has convened a number of these workgroups, and they fall into the different categories, the condition categories that we normally would screen for. The initiative started sometime early 2011. Probably started just before because the task at hand is bringing not only clinicians together from the country, but to get consensus among all of these clinicians from different newborn screening programs and academia and especially Federal entities.

I know that even though HRSA led the initiation, CDC and NIH, in particular Melissa Parisi, did -- was a focal point in making sure that all of these activities come together. The idea was

to assist in the harmonization of newborn screening diagnosis for surveillance and epidemiological purposes.

So these are the different categories that we had. Maybe I should just close this. Conditions that we were screening for here. And just I don't think the list of the committee members for the different categories have actually been recognized, or I wanted to include this slide here to make sure that -- to show that we're trying to get, working with HRSA, broad consensus on these case definitions.

So, as you can see here, this is the metabolic group, the endocrinology group, pulmonology group, immunology group, and hemoglobinopathies. So let's see here. HRSA, in collaboration with a number of folks, led the discussion about how to pretty much harmonize these conditions, the case definitions for these conditions.

And as I said over the past -- since January of 2011, they've been meeting with these

groups to discuss, to figure out how they can bring -- develop consensus, develop tables around those case definitions for the conditions that we screen for. And they've actually gone -- done a pretty good job in getting consensus and harmonizing those case definitions thus far.

A meeting was held about this, a face-to-face meeting in July of 2012. So several weeks ago, not too far away from here in another Government building. That was actually my second time in a Government building recently.

And the next steps right now is to start validating the case definitions that have been -- you know, that the groups, the clinicians in this case for the most part, have developed. At the end of the day, State public health programs will be able or would have to be able to incorporate this and see if they can actually collect the information.

And so, we're working with a number of States to see if they can beta test this, how feasible it is to collect the information, and

eventually collect this information into the NewSTEPs database that I mentioned earlier. That will be further down the line, and I will talk a little bit about that later.

I want to quickly move into newborn screening quality indicators. So the same thing for case definitions holds true for quality indicators.

In, let's see, it was March 2011, HRSA funded Genetic Alliance to fund APHL to bring together a group of State newborn screening programs to try and see how we can harmonize quality indicators across the country. These are when you think about quality indicators -- when you think about quality indicators in newborn screening, it's certainly you think about the pre-analytic, analytic, post analytic, and certainly up to short-term follow-up.

And so, we wanted to see how we can compare these from State to State to State. And so, we called a face-to-face meeting in July of 2011 and brought I think about 25 States and a number of clinicians together to discuss how we can start

harmonizing them.

One of the main activities of this was to have these States actually bring the quality indicators that they collect in their State. Sometimes it's the same, and sometimes it's different. But it was very important to see what they collect and then, using a facilitator, try to see which one of those or which of those themes are actually correlated or can be collected.

Now we have to remember that States provide this information to -- they certainly provided it to the old technical assistance resource center as a voluntary basis. This is -- there's no recommendation here. There's no funding that goes with this.

We want States to have a vested interest in putting information into a voluntary system that will help them pretty much assure their capabilities and capacities, whether it's through quality assurance or quality control or other continuous quality improvement activities that they do in their programs.

So I list pretty much some of the activities that we went through here, and this was a 1 1/2 day meeting that was quite taxing, I must say. But when you have States come up with their quality indicators, and everyone certainly thought that theirs was the best. And you know, rightfully so. But the facilitator had a daunting task of actually trying to figure out how to better harmonize this.

And this is a list of folks that attended the meeting as well. Some of you may not be able to read it back there. But again, I think it was about 25 States that attended, Federal agencies -- NLM, NIH, HRSA, CDC.

So not only did we come up with a case -- I'm sorry, the quality indicators, but tried to find ways to harmonize the case definitions that go with the quality indicators. This is going to be very important, just like the case definitions that we were working on to harmonize those.

It's very important to figure out how to -- certainly was very important to start figuring out how to harmonize case definitions for the quality

indicators that we came up with. We came up with a whole lot of quality indicators, but at the end of the day, as a consensus in the room, we were able to narrow it down to 10. And so, here are the 10, and I'll just leave that up for a quick minute here.

These are quality indicators that we want State public health programs to be able to report, hopefully, in the near future in a new database that we are going to be developing across the land. And every one of these case definitions will be the same for each one of these conditions.

We're here because of a number of reasons. Certainly, GSA has some -- the need to make sure that we have the right amount of funds to do the different activities that we're embarking on is important. And in this day and age of dwindling public health funds, it was important not only to make sure that we had an effective meeting for the case definitions that I noted in July of 2012, it was important to try and combine both of those meetings, to be cost effective.

And so, not only did we have the case

definitions meeting early on this year. We also combined that to bring States to discuss quality indicators and harmonization of those quality indicators.

I mentioned earlier that State newborn screening programs are going to be beta testing those case definitions. They will be doing the same for the quality indicators.

In fact, we had a really good presentation from Dr. Scott Shone from New Jersey, who, when we developed these quality indicators last year, took it back to his State and started the process of actually testing those quality indicators in his newborn screening to see the effectiveness of them. And certainly, he was able to not only show that this is doable in a State newborn screening program, but it was effective in assuring continuous quality improvement.

As anything, it's important to focus on the need and why States should do something that's going to be on a voluntary basis. And so, we needed to figure out exactly the importance of the quality

indicators that we were defining, the definitions themselves, if they were actually right on point and we were gaining consensus among those, and then the feasibility. Someone has to collect this information.

The last thing we want to do is create more work for State public health programs. At the end of the day, we want to make this a seamless process of putting information into the system. And so, that was pretty much the task that we focused on during the meeting. And for the most part, I think we were able to gain consensus on those 10 quality indicators that I noted earlier.

We're looking forward to working with State public health programs right now to develop a small subcommittee that will continue to refine these quality indicators. As in everything in newborn screening, there is going to be change, and we expect that these quality indicators -- at least the ones that I posted earlier -- some of them will change.

But for the most part, a good amount of

them will stay the same. We can refine the definitions, but the main idea is we want to be able to collect the same quality indicators from State to State and make sure that the case definitions that go with them are the same as well.

The case definitions for the quality indicators and the quality indicators that we developed will be the -- pretty much the backbone of the new database that we're building in NewSTEPs. Yes, this is a 5-year cooperative agreement that's been funded through HRSA.

And I don't want to -- certainly, this is the backbone, but we are going to be doing more than just collecting information and hosting a Web site for -- that will have State newborn screening data and quality indicators on that. As I noted, we're going to be providing a comprehensive resource center, technical assistance to State newborn screening programs to assure their capabilities and capacities.

We're going to engage proactively in going to State to State to see how we can assist in

helping their deficiencies. We're going to be providing a number of key educational training programs, whether it's to the laboratories or it's just to pretty much everyone in the newborn screening systems.

We have been funded, for the most part over the past decade or so, by the CDC to provide a number of pertinent activities to State newborn screening laboratories. And NewSTEPs in this new iteration will broaden our scope to provide key information to State newborn screening programs and systems across the board.

I hope I gained some time by going a little bit fast there. That's my information, and I'm delighted to take any questions.

CHAIRMAN BOCCHINI: Thank you for the presentation. It's really nice to see the progress that's been made in this area and where you are.

The several States that are participating in the beta testing, can you give us a rough number of the number of States?

MR. OJODU: Right now, we're looking at

about 13 or 14 States that have said yes to not only the case definitions for the diagnosis, but also a good amount of them for the quality indicators and the case definitions that go with those quality indicators as well.

CHAIRMAN BOCCHINI: Great. All right. The presentation is open for questions from the committee. Dieter?

DR. MATERN: Very nice presentation, but it seems to be pretty much a 30,000-foot view at this point. Where could we find out what these case definitions actually are? Where could one find examples, and what about the quality indicators? What are they? How are they defined?

As someone who is involved in a screening laboratory, I'd be interested to know so that I can apply them maybe.

MR. OJODU: Thank you, Dieter.

Good question. I only had 15 minutes for both of these, and if I started putting up all of the case definitions that were developed for each one of those categories, I think that would take a

good amount of time.

We will make sure that that is provided to everyone on the committee here, the tables that have been developed for each one of those categories of the case definitions. And then for the quality indicators that you noted earlier, each one of those has definitions that we are currently refining. And those are also available, and we can make that available to everyone on the committee for comment as well.

But, yes, it's looking very high above to see -- you know, we're getting into this. I'm not sure if Harry is here. But this harmonization of case definitions or quality indicators has been something that we've needed to do for a long time.

And I mean, I implore and congratulate HRSA and Dr. Copeland in working hard and making sure that she can bring folks together and dedicated some money to doing this. And we are hoping to gain consensus sooner than later among all of the States, and it's going to be a long process. But we're dedicated, and we'll get there.

DR. COPELAND: Jelili, aren't some of those proceedings posted on the Web site?

MR. OJODU: They should be.

DR. COPELAND: From the meeting in July of 2012.

MR. OJODU: Yes, And I'm not sure if it's part --

DR. COPELAND: I think you can see some of them already.

MR. OJODU: If you have it on your --

CHAIRMAN BOCCHINI: Which Web site?

MR. OJODU: Well, so, I'm not sure if you get the -- I sent in all of the background information that goes with this. You may not have gotten --

DR. COPELAND: In the briefing book?

MR. OJODU: In the briefing book. No? So we'll make sure that you get it then.

DR. COPELAND: Okay.

MR. OJODU: Okay. So, yes, there is a Web site that has all of this information, and you're welcome to check it out.

CHAIRMAN BOCCHINI: Jeff and then Charles.

DR. BOTKIN: Congratulations on the progress you've made on this. This looks very important, and just looking at the indicators, they seem relatively straightforward, from somebody who's not been involved in the details. I'm sure there's lots of complexities there.

But what I would wonder if we could get a better feel of is what you perceive to be the key barriers for States in adopting a more uniform set of definitions or more uniform set of quality indicators? Is this something that requires additional governing legislation? Can they make the decision at the laboratory level? What would you perceive to be the challenges at the State level for moving forward?

MR. OJODU: Well, I don't think legislation for sure. I think that we are trying to make -- the only way that States will buy into this is if they see a vested interest in doing this in the first place. How does this help their newborn screening program?

What do they get back out of putting information -- if we harmonize quality indicators across the land, what do they get back? How does this improve their program?

And a good -- every State has quality indicators, and they're already doing this. We're saying that we would like to collect the same quality indicators across the land in one place so that anyone can go in and compare or use it for continuous quality improvement.

Barriers, I mean, we're doing more with less. And some States can attest to this, and you know this already. And so, maybe it's a good question for HRSA. They are -- and the other Federal agencies in the room, they are certainly doing their best to address this problem at the present time.

And if there is a need for additional kind of assistance, and I don't know what that will be because I don't want to shoot myself now, I think that the Federal agencies will be able to address that at the time. But at the end of the day, if

this is important to State newborn screening programs, this will be something that will be, hopefully, an easy buy-in with a less amount of work on their part.

DR. BOTKIN: So do you think those States or many States will require additional funds into their system in order to be able to collect the data?

MR. OJODU: It depends. No. It requires work for sure, and that is something that -- that is always an issue of adding additional activities to a program that has been -- funding has been cut. You have those furloughs. You go through a number of other initiatives here.

But if this is important to them, we're hoping that they'll be able to incorporate it into what they currently do. Would funds be helpful? Yes. Where will the funds come? I'm not sure. But we can dream.

CHAIRMAN BOCCHINI: And then, hopefully, the manpower needs will be evaluated when you're doing the beta testing.

MR. OJODU: That's correct. I mean, that's certainly one of the major objectives of having a new technical assistance data repository program.

CHAIRMAN BOCCHINI: So Charles and then Coleen.

DR. HOMER: Thank you as well. Very exciting work. Great to see the progress.

I'll ask about the quality indicators, and this may be putting the cart ahead of the horse. On the adoption of clinical quality indicators, some of the criteria usually include not only the feasibility and does it sort of generally seem important, but whether there's variability across sites and whether there's opportunities for improvement.

Do you have any preliminary data to suggest, as one of the public commenters indicated, variation across States in these performance levels? And do you also have theories behind them as to how one can go about improving? Because improvability is, of course, another criteria for adopting a

quality indicator.

MR. OJODU: Yes, good question. I'll let Sara actually answer some of those questions.

But when it comes to State variability in newborn screening programs, whether it's laboratory or just newborn screening programs, I think it's not as big as we think it is. I think it's actually the harmonization -- I mean, there's a lot of work and effort that has gone, starting from State newborn screening programs initially to 2004, when the ACMG/HRSA report came out on harmonization of newborn screening programs and the uniform screening panel to bring that gap -- to close that gap not only in the conditions that they screen for where now that we can say that a good amount of States actually screen for a good amount of the core conditions.

So I don't think that will be an issue. And for someone who has paid a little bit of attention to -- well, a good amount of attention to the case definitions, the diagnostic case definitions that HRSA has spearheaded, the

clinicians have come across here as not only understanding that there's a need for this, but the harmonizing those case definitions is doable.

And from the tables, which you will see later, there is a good amount of consensus among those. I don't know if, Sara, you want to add anything to that?

DR. COPELAND: In terms of improvability, et cetera, those -- Brad Therell has been collecting this data since I think 1996, and we can see variability there. As one of our public commenters actually attested to, there is actually quite a bit of variability in some functioning.

And so, I think we're going to be able to measure it, and I do believe that there are places for improvement. It's a matter of making sure that it's comparable and standardized.

DR. BOYLE: Jelili, thanks for the update. It's great to hear all the work that you and others have been doing. Thanks for sharing the aims as well.

So this builds on what Sara just said, as

well as Charlie, and that is thinking back or thinking how your new system aligns with what's been done in the past.

MR. OJODU: Yes.

DR. BOYLE: And being able to track that.

MR. OJODU: Yes.

DR. BOYLE: And obviously, utilize all the good information that's been collected since whenever it was, 1996.

MR. OJODU: Yes, ma'am.

DR. BOYLE: So do some of the indicators line up between Dr. Therell's --

MR. OJODU: So some do. Some don't. And the -- I guess the issue would be those case definitions for the quality indicators. States define them differently.

And so, at the end of the day, at the bottom of all of the, you know, when you're looking at a particular condition, you are not able to actually compare them because it's defined individually from State to State. You wanted to add additional?

DR. BOYLE: I guess, just thinking from a historical perspective and all the work that went in both and from the States collecting, it would be a shame to lose some of the power of that information, regardless even if the case definitions changed somehow.

MR. OJODU: Yes, ma'am. No, no. I completely agree with you. Thirteen years, 14 years, State newborn screening programs have been putting information into the National Newborn Screening Information System for a good amount of years, and that is a treasure. And it shouldn't be wasted, and it will not be wasted.

HRSA will be providing that information to us so that we can populate it on the Web site somehow. How that is, knowing that we're developing new quality indicators. And your first question was do they match? Some do, but some don't.

And yes, we will have that legacy data that we will be able to populate on our Web site, but we will be collecting. Now that we are refining and harmonizing these quality indicators, we are

going to be moving forward with that in the new Web site that we're developing.

DR. MCDONOUGH: This is just one comment. I appreciate your presentation. I think one of the -- the number three quality indicator was percentage of newborns that were actually screened.

I think the linkage of the birth certificate and the -- that's gone before the recommendation on that to the Secretary that we'll get back next year would help meet, I think, that quality indicator. Is that correct?

MR. OJODU: We hope so.

DR. COPELAND: You know, that would be -- that's what was posited in the paper. And whether or not it's the birth certificate or a birth record, it's definitely one of the tools.

CHAIRMAN BOCCHINI: Mike?

DR. WATSON: So I'm curious about one of the intermediate quality indicators, which is the screen positive definition, because that's really where you manage the number of people that get pushed into the follow-up system.

So positive predictive value is the measure by which you know if you're performing at a level that's pushing too many people into the system for follow-up or not. And I don't really see that. Are you looking at that screen positive case definition as one of the things you're going to try to standardize?

MR. OJODU: That particular definition did cause some -- and I see people laughing in the audience because that was one of the few that was -- folks thought that was going to be a little bit interesting to collect from their perspective.

We are leaving it in now because a good amount of States said that it is -- well, from our perspective, I think it's -- we think it's important to collect. Ultimately, States will determine, as a collective, if they can provide this information to us.

And so, I don't have a crystal ball out yet. But I'm leaving it on right now because we had this meeting 4 weeks ago, and at least a good amount of people in the room or majority, let me just leave

it like that, said that this is something that is important moving on.

That's a political answer. Sorry.

(Laughter.)

DR. MATERN: I'm probably not politically correct because I think I can see how any screening programs wouldn't be able to provide that information. And I mean, I wonder do you have -- and I don't think I would have ever thought I'd say that -- a mission statement of what you actually want to achieve?

Is it to make all the screening labs happy? Are we here to help babies and families out there?

MR. OJODU: Ultimately, it's all about babies, right? I mean --

DR. MATERN: I know. I just wonder whether you have to write it down so that everybody always remembers it.

MR. OJODU: It's all about babies. So I should start off every one of my presentations by saying that. You know, it's all about babies.

Fifty years of newborn screening is coming up next year, and we're going to be celebrating the number of States that brought on State legislative-mandated newborn screening.

Dieter, the whole idea of this is to, at the end of the day, enhance newborn screening programs and, ultimately, making a difference in the lives of the children that we screen for. How we do that, using this process, using the Technical Assistance and Data Repository Program, collecting and harmonizing information, whether it's case definitions or those quality indicators so that States can -- you know, are able to compare across the land how they're doing is part of what we've been tasked with.

And so, I started off by saying that this has been something that's been going on for a while. I'm not sure if that's something that's just been there, and so, no, it's not to make anyone happy. It's to make them better at what they're doing and to help them in that way and, ultimately, improving newborn screening programs.

DR. MATERN: And again, I think, and I might just be impatient. But I think, again, screening is done for almost 50 years now.

MR. OJODU: Yes, sir.

DR. MATERN: And so, this is really nothing new, and every State lab should -- or screening lab should have an idea how to improve it if they have to and collect these data. So, to me, it's just the end of the day, which day are we talking about, and is it a very, very long day? Or could we just shorten the day a little bit?

MR. OJODU: Yes, sir.

CHAIRMAN BOCCHINI: Other questions or comments?

(No response.)

CHAIRMAN BOCCHINI: If not, again, thank you, Jelili --

MR. OJODU: Thank you, sir. Thank you for the invite.

CHAIRMAN BOCCHINI: -- for the excellent presentation and discussion.

We are right on schedule. So we are going

to take a 15-minute break. We're going to start promptly back here at 10:00 a.m.

Thank you.

(Break.)

CHAIRMAN BOCCHINI: All right. We're ready to start the next session. All right. Thank you.

We're now going to discuss the final condition review matrix. Following the presentation and discussion, there will be a vote by the committee whether to accept the condition review matrix.

This is something that the committee has been working on for a considerable period of time, and Dr. Kemper has been the lead in the Condition Review Workgroup to help finalize this. Dr. Kemper is a general pediatrician and Director of the Program on Health Services Research at Duke University.

His research focuses on the implementation and evaluation of screening programs for children, including newborn screening, screening for visual

impairment, and screening for lead poisoning. Dr. Kemper is also associate editor for Pediatrics, the official journal of the American Academy of Pediatrics. He now leads the Condition Review Workgroup.

So, Alex, without further ado.

DR. KEMPER: Thank you very much, Dr. Bocchini. I appreciate you calling it the final condition review matrix, and hopefully, that will bias everyone towards a positive vote.

(Laughter.)

DR. KEMPER: And first of all, I'd like to thank the other members of the Condition Review Workgroup, who are really a pleasure to work with and I've learned a tremendous amount from. So I really owe a great debt of gratitude to everyone listed on this slide.

So, by way of background -- I've got to over a little bit so I can see, too -- we began this process by holding a multi-partner stakeholder meeting back in April, and the goal of that was really twofold. One was to revise the process for

evidence review, and that gave rise to a new manual of procedures, which I'll talk about just a little bit, and to refine the process for weighing the evidence and formulating a recommendation, which IS going to be what I am going to talk most about today.

Again, we have this new manual of procedure that's going to help guide us through the process of systematic evidence review to estimate the balance of benefit and harm related to population-based newborn screening, to assess the public health system readiness and feasibility of comprehensive screening, something that we'll be doing with APHL, and also a clear way to communicate the review process and its outcomes to the many people that are interested in this process, including the public.

This is a slide that shows the various components that we use in the process of evidence review, going from method development to the production of the evidence reports through final dissemination. And as you can see with method

development, that includes defining well the scope of review, the analytic framework and key questions, and the protocol that's going to be used for each particular review. And then the evidence review includes the systematic evidence review, again, an estimate of the bounds of net benefit that would be expected by adopting universal newborn screening, and then finally looking at the readiness and feasibility of implementation.

And dissemination will include both a technical summary, and those are the familiar 10 million page documents that we submit to you, as well as a more accessible, but still technically correct lay summary.

So, in terms of assessing the magnitude of net benefits -- and I actually just realized I left one very important point off, which was where there's a high net benefit, that's where the benefits outweigh the harms, there can be negative net benefit where the harms outweigh the benefits. And then there's also the case where there's zero to small net benefit, and that's where the benefits and

harms are closely in balance.

And you can imagine that might occur, for example, if there's little benefit or little harm that would be expected from the screening. Or in the cases where there might be high benefit, but also high harm. Both of those end up, through the magic of subtraction, with zero to small net benefit.

Now notice when we talk about issues related to net benefit, we're not looking at costs here. Costs are really separate. It's a component of feasibility, and I'll be describing that in a little bit.

As we go through the process of assessing what we think the net benefit is that might be associated with screening, you also have to consider how certain you are about these findings. And again, this can range from low certainty where the available evidence is insufficient to have confidence in the assignment of net benefit because of limitations in the available evidence, to moderate certainty where you can imagine that

further research could change the magnitude or direction of the findings with any of the key questions that are looked at, such as the overall assessment of net benefit would change.

And then there's high certainty where your assessments of the net benefits is unlikely to be strongly affected by the results of future studies.

And this is Matrix Number 1, and I'm going to be presenting yet another matrix and then what I call the mother of all matrices, where things are combined. And so, you see on one side, the certainty of net benefit, as we discussed before, of high, moderate, and low. And the magnitude of net benefit, significant, small to zero, and negative. And I've given each of these a letter kind of grouping them.

So with -- in terms of making a decision, obviously, the best place to be is if there's significant net benefit and you're highly certain of that, but also important could be the case where there is significant magnitude of net benefit, but you only have moderate certainty.

You can see that in this table there is low certainty. It doesn't really matter which category you're in. Things can change a lot.

And again, I've grouped the small to zero net benefit between high and moderate, and negative between high and moderate certainty as well. Again, we're going to be revisiting this in a little bit.

Now in terms of assessing the state of readiness, and again, this is going to involve a lot of qualitative thinking as you make decisions about it. But you can imagine the setting where things are really -- where public health systems are ready, that they could implement the screening within a year if the resources were available.

You could imagine developmental readiness where most public health departments would require maybe 1 to 3 years to implement screening even if the resources were available, and potential barriers can include, for example, the need to develop high-throughput screening. So the screening test may be developed, but it may never have been tested in large health departments where, obviously, high-

throughput screening is critical. Or the equipment, supplies, training materials that are required for implementation need to be refined or just made available.

And then the lowest category here is unprepared, where most public health departments wouldn't be able to implement the screening in fewer than 3 years.

Now contrast that with issues of feasibility. And again, I've broken feasibility up into just two levels. High to moderate feasibility where screening is possible within the financial constraints of most public health departments, and the cost of screening is well balanced against the other obligations of public health departments. To low feasibility, where the resources for screening are not available to most State public health departments or the cost is not balanced against the other obligations of most State health departments.

And I appreciate that making these decisions is going to -- there's not a scientific answer. I'm not going to be able to say this is

high to moderate feasibility with this score and this bounds. I mean, this is where the deliberation of the committee is really going to come strongly into play.

But you can imagine -- you don't even have to imagine because I have it listed here -- a second matrix where you have readiness, as I discussed before, ready develop or developmental or unprepared, and then feasibility, high to moderate and low, and I've classified these things into four categories. And again, if the feasibility is low, you can see how I marked that across the various categories of readiness.

Now the key thing here is that the combined matrix is a guide to support the development of specific recommendations. It alone doesn't specify exactly what the recommendations of the committee are but provides what I hope is a more transparent way to discuss this. And also as we present the deliberations of the committee to the various stakeholders, including the public, they can really understand how it is that the decision got

made.

So here is the combined matrix, and I should really thank K.K. Lam for putting this together. And I've been joking with her that what we really need to do is hand out 3-D glasses to everyone to look at this because we're looking at things across three dimensions.

And you can see on the top readiness and the other categories. The key things really here that I want to point out are A1, right? So everybody wants to be A1. That's where screening for the condition has a high certainty of significant net benefits. Screening has high or moderate feasibility, and most public health departments are ready to screen.

Well, that's the no-brainer situation, and then you can see that A2 and A3 moves across the stages of readiness. With A4, there is high certainty that screening would have a significant benefit. However, most health departments have low feasibility of implementing population-level screening.

And you can see how as you move across these various categories, it can really help with the development of the recommendation by pointing out, for example, to the nominator what the particular gap is. Or in contrast, when you're making recommendations to the Secretary about what you think the health departments ought to do in terms of screening, you can point out that where things are in terms of readiness and feasibility and what the net benefit is and how we expect this to play out as screening is adopted.

So you should have all this in your materials as well, which I think will help as you move ahead with voting. But I do also want to point out this is in our manual of procedures about how to do things, but having a standardized way to communicating this all is very important.

So this is not something that you need to vote on, but I just want to illustrate how it might play out. So you can imagine a table that would come out after recommendation that would include the nominated condition, what the available screening

methods are, whether or not it was recommended to be added to the RUSP, what the evaluation code is based on the matrix, what the evidence gaps are related to the net benefits. And there will always be gap there.

What the public health system readiness and feasibility needs are, recommendations for future research, recommendations for future public health activities. And then our rationale that could be easily accessible by the various stakeholders, as I've talked about before.

So here's a proposed committee use of the matrix, and I thank Dr. Bocchini and Dr. Copeland for help formulating this as well. But you can imagine the conditions that fall into categories A1 and A2 would be those that would be recommended for adding to the Recommended Universal Screening Panel.

Those in A3, A4, and B would be ripe for an expedited review after whatever the particular gaps are are addressed by the nominator or until such evidence comes forth that it's clear that those are addressed. And then, if you fall into the C, D,

or L, then resubmission would be required for consideration to the Recommended Universal Screening Panel. Again, falling into C, D, and L means that there is important significant gaps that would prohibit the committee from recommending that it be added to the Recommended Universal Screening Panel.

So this is the proposed vote. I don't know if I'm like breaking the rules by reading this slide. But a vote of aye would mean that the Advisory Committee supports the use of the new decision matrix to guide the development of recommendations regarding the RUSP. And then nay would be that the Advisory Committee does not support the use of the new decision matrix to guide the development of recommendations regarding the Recommended Universal Screening Panel.

I think I read those with equal intensity and didn't bias anybody in my reading of the options, although I think I know where everybody wants to vote. So I will turn the floor back over to Dr. Bocchini.

CHAIRMAN BOCCHINI: Alex, thank you for

the presentation. It really helped clarify the issues very nicely.

And I think to remind the committee, we did look at an original draft of this at the last meeting and had input into further development. And then Alex took that back with his group and then worked further to put it all on one page.

And so, I think this really represents significant amount of work and adds the public health impact that we had not included before, and it was something that we were directed to go ahead and do, as well as, as he said, creates a significant improvement in the transparency of how the decisions are made and then categorized.

So let's open to discussion. Cathy first.

MS. WICKLUND: Thanks, Alex.

That was obviously a lot of thought, and I apologize I was not here at the last meeting. So if this came up, my question, I'm sorry.

How do you propose that we assess the readiness from the public health departments, and where is that data going to come from? That is not

going to be from a literature review?

DR. KEMPER: Right. No, that's a great question. We did talk a little bit about that last time. But our plan is to work with APHL, who are then going to reach out to public health departments and collect both the qualitative and the quantitative data to give insight to that.

Because you're absolutely right. This is not the kind of thing that you can find from published work, and I will tell you that Jelili has been really thoughtful in coming up with a plan that can be done in a relatively short period of time. And I think that our partnership with the APHL has really allowed us to do that.

Because I don't live in the public health department world, and so I'd be the wrong person to be doing that evaluation as well.

DR. HOMER: Thank you, Alex.

And I was at the last meeting. So if I'm asking questions that we asked before, it's just because memory is faulty as I age.

So, really, two specific questions. So

one is how confident you are that readiness and feasibility really are separate dimensions because they seem -- I sort of conceptually get, yes, they're a little bit kind of, sort of different. But I bet they track?

DR. KEMPER: I absolutely think that they're going to track, and this is something that we really wrung our hands over a lot before. The reason that we ended up separating them is because I think that they both need to be carefully considered.

I think, again, I agree with you. I think and a lot of times it's going to track, but I think that if we don't separately consider them that we might miss important nuance. But it could very well be that in the future, after we use this format, assuming that we go forward, that it will be changed.

I think that that's one area that I have of concern. But what I'd ask is if we could at least go ahead and try this process and then, if it doesn't work, revisit it. But they are very closely

linked.

DR. HOMER: I guess related to that, and I know we did discuss this last time, is our comfort -- because this relates to not only sort of finding the information, but using it for decision-making. I'm highly conscious of the difference between what the U.S. Preventive Services Task Force uses, a process I know you know well, and what we're using.

And I distinctly remember, for example, recommending that depression screening be universally done even though we knew that the healthcare system did not yet have the appropriate resources yet in place. And we quite -- we made a very conscious decision at the U.S. Preventive Services Task Force at that time to use that recommendation to drive health system performance.

So I'm just wondering how that plays out here, where we're saying, yes, well, they kind of can't really do it yet. So we're not going to recommend it. Is that going to keep us from driving the performance of the public health system in a way?

DR. KEMPER: That's just a very great and insightful question and something that I've shared this material and have had input both from Dr. Moyer and Dr. Calonge, both former chairs of the U.S. Preventive Services Task Force. And of course, Dr. Calonge has been involved with the community guide.

And I do think that that's an important question for the Advisory Committee to determine the degree to which it wants to push things. So things may not be ready or there may be questions about feasibility, but go ahead and push things versus waiting until things are more in place and get things going.

I think that there are different ways of going about doing this as well. I think that one of the very powerful things that this Advisory Committee can do is push for statewide pilot studies, for example, like what was done in SCID. I think SCID is actually a great example of that.

You know, it's kind of funny because I always hate the word "pilot study" because at least in the clinical world when we think of pilot

studies, we think of like a study with just 10 people and over a short period of time. But obviously, these pilot studies are very difficult.

But I think that that's one option that the Advisory Committee does have to be able to push the envelope. But again, I don't live in the public health department world -- maybe Dr. Lorey could comment on this -- that I'm sensitive that I don't want to push things too much either because of the obligations that public health departments have.

So I think that, ultimately, the decision about whether or not we push States that may not feel like they're ready versus wait until there's more material before we go ahead and recommend it is something that's in the purview of the Advisory Committee. But I'm hoping that at least by classifying where things stand at the time that that can help at least inform what the decision is and what you're pushing for.

Does that make sense? That was a little bit more of a long-winded answer than I meant to give you.

DR. HOMER: It make sense, but it means we need further conversation about it, I guess, as a committee.

CHAIRMAN BOCCHINI: Right. And I think if you'll show the next slide, because in addition -- I'm sorry.

DR. KEMPER: The next slide?

CHAIRMAN BOCCHINI: One more, the proposal. Oh, back one.

DR. KEMPER: Back one? Very good.

CHAIRMAN BOCCHINI: Because this is the next step. And so, the goal here is that to try and use this in the best way is to indicate that sort of the no-brainers here, the A1 and A2 are clearly going to be accepted by the committee as being appropriate and voted positively.

But then, when we get down to the other categories where there is missing data or other things that are needed that would be brought forward by this process, but this leaves the committee with the final decision. The decision is always the committee's. And so, we can go out of these boxes

depending upon how the committee feels relative to the issue that you brought up.

So I think that's important. It doesn't lock the committee.

DR. HOMER: That's really the question. Are we -- when we're voting on the matrix, are we locking on this? Or are we -- because this says -- really limits our discretion to some extent if you're in that middle category.

DR. COPELAND: Well, and that's where we -- part of the goal of even having this slide was we need to come to a consensus. And you need to come to a consensus on what will go forward to the RUSP and what won't so that we can stick to it.

And that's been part of the concern at the level of the Secretary is that in comparison to the USPS Task Force is that there's guidelines in that if it falls into whatever recommendation level, you stick to it. And so, if you -- you can change these levels, but I would ask that we come to -- you come to a consensus and vote on where you think we could see it going forward to the RUSP and could not.

Because we need to have something concrete in which to vote on in the future. We can't be changing where we think things fall depending on the condition.

CHAIRMAN BOCCHINI: I think -- just to further clarify that, I think it's as the data is evaluated, there will be some discretion as to which category to put them in. But the goal is to have the category so that once it's in that category, to then have the decision made by the category it's placed in.

So it is committee decision, but it is based on the category. So --

DR. HOMER: I do read these criteria as stricter in a sense than the U.S. Preventive Services. So particularly B, again, if I recall the U.S. Preventive Services Task Force, you know, the different levels of evidence and confidence, B still says there is a moderate degree of confidence that there's significant benefit, and we're not recommending.

I think that would actually at the U.S.

Task Force still lead to a recommendation, and this is leading to almost the equivalent of an I recommendation, insufficient evidence to go forward. So I am struck that the threshold looks a little higher to me.

DR. KEMPER: Well, I know that the task force really struggles about the B rating as well. So it's my understanding, and maybe this has evolved since then, but that the B may be going away anyway. That's at least what I've heard.

DR. COPELAND: And these aren't meant to be the same as the U.S. Task Force. These -- well, yes, because we have to do the public health impact, and the task force doesn't have to. But not only that, but our gradings A, B, C, they're not meant to be equivalent here. Yes, these are -- we just happen to have the same letters.

DR. KEMPER: I can change it to W, X, Y.

DR. COPELAND: Yes.

CHAIRMAN BOCCHINI: Fred and then Dieter.

DR. LOREY: Yes, just along the same line of discussion about category B, an expedited review

will occur after noted gaps are addressed. So what we're saying then is if there's a moderate certainty that there's a benefit despite what we have in feasibility, by expedited review, do you mean the nomination and prioritization would send that forward? Or are you talking about the wide vote?

DR. KEMPER: I'll let -- I'll defer to Dr. Copeland.

DR. COPELAND: This would come after nomination and prioritization. This is after full condition review. And so, once the gaps are identified, it would go -- it would come back to the committee and probably to the evidence review or the public health impact review in an expedited manner, but it wouldn't have to go through the full process again.

CHAIRMAN BOCCHINI: So we had Dieter and then Coleen.

DR. MATERN: Yes, I still have the same concerns I had at the last time's meeting about all these As. I think if we find or the evidence review finds that a condition has high benefit, there is a

screening test, and the only issue might be that the States are not immediately able to implement this. And basically, then given it an A3 or A4, it would be delayed until the States actually pick it up.

If we look back at the uniform panel, if we didn't have the uniform panel, whatever, 6 years ago and would have maybe put everything into an A3 or A4 category because not everyone had tandem mass spec at the time, we might have a room full of mothers whose babies died of MCAD deficiency.

So I don't think we're doing anybody a favor by saying, well, let's hold back because the States are not ready.

On the other side, if you do that, you might have a situation such as for Krabbe disease where a State suddenly has to do something because of a local process, legislative process where they have to provide Krabbe testing, even though this committee thought it is not yet ready for primetime.

And as you all know, last week Missouri started to screen for Krabbe disease, although they're totally unready and basically had to

outsource it to New York. So I don't know if you want to kind of have more of such situations.

I think if there is a condition that we feel can be screened for, should be screened for, we should suggest that to the Secretary and not say, well, you might just say you should if you can. I don't think that's a good solution.

DR. BOCCHINI: Coleen?

DR. BOYLE: So I think we're all talking around the same issue here, and first of all, I want to say wonderful job trying to put all of these concepts into one matrix. But at the same time, when I think about it, I actually think of it in a staged way. And this matrix that combines everything doesn't allow me to do that.

So, for me, I think of looking at the first matrix as really the net benefit. That's the science that tells us whether or not there's actual evidence to show benefit. So that, to me, is stage one in my mind. That has to be in place.

And then the next level, once we are there, then we talk about the readiness and the

feasibility aspects of it. So even though you're trying to combine them all, and I appreciate that, in my mind, I don't combine it. It's -- and that's where some of the art comes in, I think, in terms of saying whether or not we want to push the envelope a bit or not.

And so, I was trying to make the analogy between efficacy and effectiveness perhaps, and I feel like that's a stage process in this matrix. And I think we still could use the matrix, but at the same time, I feel like it blends those things together too much.

Let me just finish. One more thing.

DR. KEMPER: Oh, okay. That's good.

DR. BOYLE: And then I don't like the orientation of the matrix, where readiness is up on top. I actually feel like the net benefit piece should be the overarching factor if you're going to use this one big matrix, where somehow you get the readiness and the feasibility into it.

So, anyway, those are my thoughts.

DR. KEMPER: Okay. Poor K.K. is going to

die if she has to reorient it. Let me, if I could just address the issue, though, that you brought about why it's a combined matrix instead of two steps.

Earlier in the process, we had actually considered it to be a two-step thing, but there was no sense looking at readiness and feasibility until you knew about what the net benefit was. And the reason that we moved away from that is because we were worried that if we went to this committee and the committee finds that there's significant net benefit from screening and then we move to do the feasibility assessment, that that puts us off essentially by a meeting.

And so, we didn't really think that that was fair to families if there is likely to be a strong benefit from screening and then we had to wait to do this readiness and feasibility assessment. So we decided that we would work with APHL and do everything in tandem. And then as we realized that we would be doing everything all together, it made sense just to pull things up.

But I absolutely agree. I mean, there's no way to look at that other complicated matrix and make a decision. So that I would encourage its use, that there's like a proper use, if I'm allowed to say that, is to go through the first matrix and then go through the second matrix.

The big mother of all matrices was just a way to communicate where things finally ended up. But I wholeheartedly agree with you, Coleen.

CHAIRMAN BOCCHINI: Jeff?

DR. BOTKIN: Yes, this is excellent work and very helpful for me to help organize my thinking about these kinds of things. But I am sensitive to this notion of readiness and whether that -- and feasibility and whether that turns into a reason not to proceed when, in fact, States need to be pushed to proceed.

And so, I guess one additional layer of complexity there that may be fairly obvious is that States are going to exist across a spectrum in terms of feasibility, and you may well have some vanguard States who are quite ready and able and many other

States who would be quite resistant because they're not prepared.

So not quite sure how the assessment would occur in that particular domain, but it also seems to me that the matrix is one thing. How the matrix is used to make a recommendation is something separate. And I want to put up that slide for just a second.

It seems to me that the slide that incorporates which categories might lead to which recommendations, right? It seems to me that that -- this is where some of that debate might occur in terms of what the implications might be for the data analysis in this sense in terms of what sort of recommendations.

And it seems to me in certain circumstances, the committee might well say States aren't ready, but that's okay because they need to get ready. Whereas, something like congenital heart disease, which I think prompted some of this discussion around feasibility, was a paradigm shift for States. And I think a lot of States were upset

to say, well, we don't know what we're doing with this whole new type of bedside screening.

So I think that's a different type of feasibility consideration. So one last question. It might not be entirely fair.

Have you had the opportunity to sort of test drive the matrix with recent conditions, and have they been illuminating for you and reinforcing in terms of how the committee approached those issues?

DR. KEMPER: So I can tell you that informally as a group we've done that. I don't know if that's a fair enough test drive. I mean, I think that, ultimately, the test is going to be in putting a particular condition up into it, a condition that might be under consideration like Pompe disease. Not to push things or whatever.

But we did, you know, you're exactly right that it was the screening for critical congenital heart disease that really made us step back and thing about this process. And informally in the group, too, we did kind of think about where

different things would fall.

But it's my personal feeling that the best test is going to be to try to do a condition prospectively and find out how well it works. Again, as I told people that the matrix did not come to us from Mount Sinai, and it's not immutable. And I suspect that it will change.

I think that, for example, Dr. Homer's comments about the relationship between feasibility and reliability is important. Another issue that you brought up in your comments was which States do you look at when we consider feasibility and reliability?

You know, it's not our plan to look at the States that are resistant or laggards in adopting whatever particular screening technology or screening service that it would be, but to really look at the ones that are more on the cutting edge, maybe a couple in the middle.

But I think that there is going to be a lot of lessons to be learned from doing exactly what the kind of work that you describe. But it would be

my hope, too, that we would be able to have some agreed-upon format to at least put the conditions in as we go forward.

And you know, I'm very sensitive, too, to the comments that Dietrich made. And it's not my intention that if there's a particular condition for which there is overwhelming evidence that screening leads to lowered morbidity and mortality, but States haven't adopted technology that's otherwise available, that we use that as an excuse -- and I use "we." I'm not recommending anything.

But that you all -- that that will not be a reason not to add something to the RUSP. I used too many "no's" in there, but I think you understand what I'm trying to say.

DR. TARINI: I'm speaking now as an individual, not as the liaison of the AAP. I have one comment and one question following up on this discussion about feasibility.

I guess my comment is I sympathize with the concern that a condition with overwhelming evidence could perhaps be more slowly implemented

because the States say, well, I'm just not ready or I don't have or I can't. But I would argue that from the practical view, that's what happens.

And so, to delude ourselves that while we don't formally look at feasibility and we recommend a condition, the fact that feasibility doesn't play out in the real world, hasn't been playing out with SCID, is a bit of a delusion.

And so, in some ways, having this information available for the public, I would argue helps them to understand perhaps the complexities. And as Dieter pointed out, we're here for the public service and to help the children and the families. And I think if they understand the complexity of the process and what needs to go into implementing a disorder, regardless of what its evidence base is, I think that's helpful.

My question is as to the implementation on this slide. If we're talking about public health feasibility, why is it the nominator's burden to address the gap? I feel like it might be a bit of a disconnect.

For instance, let me be concrete. If a State does not have a specific, very technical machine necessary to do a test, why is that gap addressed by the nominator? It seems to me that that's more of a systems-level technical issue perhaps better handled by the committee or at the public health level or at the national level.

CHAIRMAN BOCCHINI: That is a good point. We can discuss that further, but let's go to Cathy.

MS. WICKLUND: I was just going to -- you covered my point, Beth. I was also concerned about how that person would actually be able to change the feasibility or readiness at a State level.

DR. COPELAND: But keep in mind, too, not to say that isn't a burden. But rather keep in mind we're not just looking at one State. We're doing a survey of States, and it's going to be the average of where things stand across the nation. It's not just going to be, well, this State says they can't do that so, therefore, it falls into this category.

So, again, it's hard when we haven't shown you how it can and should work. But again, I think

that it's not just going to be one State. I mean, they're already on a State-by-State basis. So the public health impact is going to be a survey across the nation looking at a variety of States. So --

DR. KEMPER: And if I could just re-emphasize the point, too, that it's going to be done by people who really understand like how laboratory stuff works.

So, for example, if I went in and asked like is this track DNA-based test hard to do? Everyone's going to say yes, I'd believe it. But by having people who are really knowledgeable about these things, we'll be able to provide a different level of rigor and understanding about this.

CHAIRMAN BOCCHINI: I think we have Melissa next.

DR. PARISI: So my question is about how this might impact the nomination form or at least the nomination process? I know that at the last meeting, we discussed revising the nomination form.

I'm just wondering whether any of these public health impacts, such as the feasibility and

the readiness, would be incorporated into nomination form, not so much so that nominators would be expected to do a rigorous review of those factors, but so that they would be aware that that would be part of the review of the condition?

DR. KEMPER: That's a great question. I'm going to actually defer that to Dr. Lorey, who's on the Nomination and Prioritization Workgroup. You like that, huh?

DR. LOREY: Could you repeat the question, please?

DR. KEMPER: Just, I mean, does the nomination and prioritization process and form need to change to incorporate the feasibility and readiness component so at least the nominators can know that that's going to be an issue and be able to present some information about that? I mean, it seems like a reasonable thing to do.

DR. LOREY: Well, that was sort of the nature of my first question because looking at these categories and their descriptions as you presented, sort of following the same procedures could change

the vote of the Nomination and Prioritization Subcommittee about it.

So it's almost like we need the same guidance because it's like you're addressing in category B nominations that we might not have put forward to the greater committee.

DR. KEMPER: Yes. You know, it's always dangerous for me to think in front of a crowd. But the other thing is I'm just thinking about it in terms of the evidence review.

You know, even if there is still -- and this gets to Dr. Matern's comments before, too, that even if there are questions about feasibility and reliability, if it turns out that screening for the condition might lead to significant benefit, then maybe that that would be enough for it to go through the Nomination and Prioritization Workgroup to us.

And then going through the two-step dance, as Coleen mentioned, although I don't think she called it a dance, if it turned out that screening was highly beneficial, but then there were these questions around readiness and feasibility, that's

really -- that's an important message to get out and to have people work on figuring out what would it take to move health departments to the position that they can screen for things.

So, you know, Dr. Parisi, again I apologize for thinking on the spot. But again, maybe that readiness and feasibility stuff should come after an assessment of the degree to which there is evidence to support it. Or maybe I'm wrong.

DR. PARISI: I guess I'm just advocating for there at least being recognition of that so that when nominators submit their forms that they're aware that this is part of the evidence review.

DR. KEMPER: That those can be addressed. I totally agree with that.

CHAIRMAN BOCCHINI: Yes, I think that's a good point, and I think that the Nomination and Prioritization Committee is looking at a degree of information that if we meet set criteria, then it's going to go forward for the full evidence review. So that all of the Nomination and Prioritization

Committee does not really perform an evidence review. It just determines whether the packet of information contains the information that is required to move forward to an evidence review.

So it will not have everything, but I think Melissa's point is really well taken that the nominator needs to understand what, if it moves forward, is going to be -- or what one is needed for the Nomination and Prioritization Committee review to accept that nominated condition and bring it forward to the full committee for a vote to move forward to evidence review, and then what the evidence review is going to require for the condition to then come back and fit into the category where it will be accepted.

So I think that's a good point, and that needs to be a part of the whole packet of information that the nominator needs to have. So I think that we can clarify that.

DR. LOREY: Right. I agree. Because I think in some cases, the Nomination Committee may put a lot more emphasis on things other than the net

benefit than you see here, and that needs to be known.

CHAIRMAN BOCCHINI: Right. That's good.

So we have Steve, and then we'll go back to the audience. And Dieter? Okay.

DR. COPELAND: And Carol.

CHAIRMAN BOCCHINI: Carol? Okay. Well, let's do Steve and then Carol, then Dieter. Okay. Oh, and then Charles? Okay.

DR. MCDONOUGH: Thank you.

I like the matrix you've put together, and I think we all would look at things differently in making decisions. But as far as how we categorize things, I think it's really good.

I'm not ready to support this proposed committee use of the matrix. I think there may be B1s, A3s that we ought to approve, and so this is the area I have concern with at this point. And I think this requires a lot of discussion. I don't know if we're going to be able to meet consensus on this.

But as far as using this as an

organizational tool, I think you've done great work, and I'm very happy with that. This is a big philosophical question about what our role is and if we're going to be a leader or a follower. And if we're going to be doing anything over the next couple of years or if we're going to just tell people to go back and do more research.

So this, I think, is very important, and I'm not prepared to support this at this point.

CHAIRMAN BOCCHINI: All right. So, Carol?

DR. GREENE: I don't know if other people would agree, but I think that the point that Beth raised is almost -- it's not just semantics at all, but it's an important different way of looking at the same question that was raised. And I do notice it doesn't say that the nominator has to resolve the gaps, just say they have to address them, which would mean they might explore them and say here are the gaps. But I think it's sort of, in my opinion, ridiculous that the State can't just buy a tandem mass spectrometer, a TMS machine, because look how much money they're going to save in kids' lives.

So I'm not so concerned, with due respect, to the asking the nominator to point out the gaps or address them. And I think that really brings us back to the question of do you lead or do you follow? And I am really uncomfortable -- I mean, I know I don't have a vote. But I'm very happy, again, with the matrix, but I'm uncomfortable with this without having some resolution.

And perhaps the issue would be some very explicit clarity writing out which States would be reviewed and how, and what are the criteria for determining is it feasible? Because what I heard is a lot of great thought has gone into it, but it's not written down. And that would be an opportunity to revisit what we've done before, which is sort of different criteria for different people.

So if it's something laid out that says X number of States and looking at the leaders and looking at -- because also is it population? Is it number of States? Is it the wealth of States? Is it different percentage of population?

So I think it needs to be addressed in

much more detail.

DR. GETCHELL: Okay. To follow up on that, I do believe it's really important to survey a broad swath of States for readiness, and I think that's a very important indicator. And not just laboratories, but programs especially as well.

And I think one of the purposes that that will accomplish is sort of raising the awareness of States that this is on the horizon, and they need to be thinking about it. Here we are, a year and a half after SCID was recommended for the uniform panel, and I think there are many, many States that still have not implemented it. It just takes a long time. Not just for the laboratory aspect, but for the programs aspects and the approval in the State legislature.

So if States are broadly aware that this is even being considered, I think they will begin to prepare.

CHAIRMAN BOCCHINI: Thank you.

Who else? Dieter was next.

DR. MATERN: So that, I guess, brings back

the point that if we put, for example, SCID in an A3 or A4, the pressure on the States wouldn't have been there because they didn't really figure, well, at some point we have to deal with it, but not right now.

Coming back to Beth's point about transparency and making the public aware of why things are not happening as fast as the parents might want them to go forward, or me, I think I totally agree with that. I just don't know whether this committee or on the Federal level you have to do this explaining. I think it's the States that have to explain why SCID is not yet implemented.

Again, coming back to Missouri, I think that the State lab had, from the get-go, and they got their law on the docket that they have to screen for Krabbe and for other LSDs, have told the people that Krabbe is not part of the initial screen because a test is not ready. They wouldn't have had that conundrum where they suddenly within I think 6 weeks or so had to come to a process to screen for Krabbe in Missouri.

So I think it's on the State level that the State labs and programs have to be transparent of why they're doing things and maybe why they don't do them yet. But we should, again, I think concentrate on can it be done, and is it worth doing? And that should be our recommendation.

DR. COPELAND: Except for our legislation says we have to have the public health impact analysis, and that was the charge from the Secretary with the CCHD letter as well is we need to have that analysis done before we add things to the RUSP.

CHAIRMAN BOCCHINI: Charles?

DR. HOMER: So I guess I have one and a half specific recommendations or suggestions or modifications. So one is going back to the earlier point I made. I think we should view category B as we do category A.

So to the extent that we differentiate and particularly in the decision-making process, given the general medium to poor quality of evidence in this field, I think moderate certainty is pretty good. So that would be my suggestion. So that's a

specific suggestion for changing the matrix.

The second is let me draw another analogy not to the U.S. Preventive Services Task Force, but to another group that I'm very actively involved with, which is the implementation of the Child Health Insurance Program Reauthorization Act quality measures. And that was another activity where the Federal Government, in this case CMS, or the Secretary actually has adopted a number of measures which she wants the States to use.

And similarly, to other situations, the Federal Government, of course, can't dictate to States what they do. And so, they are spending a fair amount of time and effort and money providing technical assistance to States to facilitate the implementation through a number of contracts analogous to the APHL technical assistance contract.

So I wonder if we can either have an intermediate recommendation or a recommendation that goes along with the recommendation to putting something in the RUSP that if it is A2 or A3, we add on that this be incorporated into a technical

assistance program.

And something along the lines that acknowledges that, unlike an A1, B1 recommendation where it just goes in and States can do it. That A2 and A3 is associated with a developmental process and a technical assistance program that goes along. And again, that may be outside the purview of the committee, and I --

DR. KEMPER: Similar to what happened with CCHD.

DR. HOMER: But it is similar to what happened with CCHD. And to me, it seems to make sense.

DR. COPELAND: It's the committee's vote, and so, I mean, that's definitely something you can put in there. And I think that it's also in line with SCID. What we did with SCID is we sent it back and said let's at least detect a case. And so, I think that's well in line.

The availability of funding is a different issue because it's not just quality measures. It's actually implementation. But it's definitely

something that the committee can recommend.

CHAIRMAN BOCCHINI: All right. Does that adjustment satisfy some of the concerns that were raised, especially by you, Steve?

DR. MCDONOUGH: Mr. Chairman, I'm ready to support this right now. I mean, that this is our way that we think through things and categorize them.

And there's been tremendous work done, and I think changing As and Bs and stuff like that, I think everyone can have a different perspective. So I'm ready to support that.

This, though, I think requires further discussion. And either we vote on this separately or we think about it, we amend it. But just as B1s and B2s I think ought to be supporting those, and if there's a moderate degree that this is going to help and the health departments can do it, I don't know why the heck we wouldn't recommend it.

I mean, I view this committee as a leader that my expectation is if we approve something, if States can do it in 3 or 4 years, most of them,

that's darned good, okay? I don't expect them to do it the next year.

I've worked in a health department for 15 years. It takes a lot of -- long time to get things done. But you don't -- you lead and you don't let the people who can't get things done hold you back.

And if there's a consensus today that people feel that way, then I think we ought to vote. But this is a really, really important discussion, and so I'm ready to move support of the matrix for decision. And, but I'm at what your perspective, Mr. Chairman -- Dr. Chairman would be on how to do it.

(Laughter.)

DR. MCDONOUGH: But that's what I would like to do. I'd like to vote on this. So all the people on the As, Bs, and stuff we can have a consensus on that. And then the real discussion I think will be on what we do.

Again, my perspective, B1 and B2, we ought to be approving those. I think a lot of the A3s, I think we ought to be approving those as well.

And we may, if we can't come to a consensus on that, then we'll just hash it out over the next couple of years when these things come up and we say, okay, this is A3. How many ayes and how many nays do we get? And then we'll find out.

CHAIRMAN BOCCHINI: Well, I think if we go back to what the definition was for the moderate certainty and how to get to a B category, I think it would be difficult to make the recommendation that we would always approve a B category. I think that there may be enough of a gap where additional data is needed. We needed to find a positive for SCID, as Sara just mentioned.

So I think that if we say further research could change the magnitude or direction of findings within any of the key questions, such as assessment, net benefit would change, that's enough for us to be concerned that in some cases we would not want to go forward with that. And so, I think that's why I would not want to make a blanket statement that B would be acceptable routinely to go forward.

I think there might be gaps that we need

to have settled before we can make that decision.

DR. MCDONOUGH: Mr. Chairman, but I don't want us to be held back because we say it's a B1 that we cannot vote to support it. We may have to individualize and hash that out.

But I would oppose any effort, if it was a B1, to say any B1 we can't support.

CHAIRMAN BOCCHINI: Right.

DR. MCDONOUGH: I think that would be bad.

CHAIRMAN BOCCHINI: All right. Other comments from the committee concerning that specific issue?

Jeff?

DR. BOTKIN: Quickly, I agree with that, and I do think quite a bit more discussion about how the assessments based on the matrix would be used for decision-making. I do see them as separate things.

I do think that we can probably draw some lines. I mean, I think C or below I would say that is not ready for screening. But anything in the B and above might well be approvable, depending on the

particular combination of factors in terms of data and feasibility that might be relevant to a particular case.

DR. BOYLE: I guess I would want to float the motion of separating the two matrices. Yes.

CHAIRMAN BOCCHINI: I'm sorry, you would?

DR. BOYLE: I would like to put forward a motion of actually separating the net benefit and certainty from the readiness and feasibility. Just from a conceptual standpoint and a voting standpoint.

CHAIRMAN BOCCHINI: Okay. So we have a motion then to separate the two matrices, one for the review of the condition and then second for the decision on whether we have a formal decision made as a result of that categorization.

DR. BOYLE: And my rationale there is that I think it's going to depend on the condition. So it's hard to put them all in one big matrix. That's all.

CHAIRMAN BOCCHINI: Right.

DR. KELM: Can you -- are we going to

separate the reviews? I mean, Alex suggested that we would actually have to separate them from meetings, or you think we would still have all the review done and still start with net benefit and then move on and do it one meeting? I think we'd also want to --

CHAIRMAN BOCCHINI: Yes, I --

DR. KEMPER: Right. I guess I'm just asking the committee. You know, it's certainly easy to separate the things, and I can envision two votes. But I would ask the committee if you want us to do the readiness and feasibility assessment in the process of doing the other component so that when it comes to a vote, they could both be done at the same time.

Or if something -- if it turns out that the net benefit is such that it doesn't matter what the readiness and feasibility is, I can imagine not specifically address it. But for completeness sake, would you like us to, regardless as we're putting together the evidence, because we don't know where things are going to play out, to complete both

products?

CHAIRMAN BOCCHINI: Yes, I think the decision had already been made to have a single presentation of the data in a complex way rather than doing the benefit first and then coming back. If the committee agrees to benefit, to then do the public health evaluation. So I think that's pretty much set.

So what we're really talking about is dividing this from the next slide, which was once you've made a category, that the decision was pretty much locked in about what the committee would do. So, and we're really talking about essentially the A3s and 4s and the B categories as rather than saying there's a definite delay in a decision, as opposed to the committee might decide to move forward with some of those decisions based on the condition or what the gaps may be or whether it's primarily readiness as the primary issue.

So I think if there's no more discussion -- Melissa?

DR. PARISI: Quick comment. I mean, could

you do both? I think some of it is a conceptual difference. And if you had the separation of the matrices as one way to look at it and then also tried to combine it into one matrix to sort of do a consolidated attempt at determining where a given condition fell, then that could be valuable to different constituents.

DR. KEMPER: Right. So just if I could -- I'm sorry. I'm probably breaking the rules here. But so I would imagine that, I mean, the actual process would obviously have to be a two staged vote, but in terms of like a grid where I had that would communicate the deliberations of the committee, it would be a combined letter and number. But they would just see those two things together.

Is that -- Coleen, is that concept right?

DR. BOYLE: That's not the way I would like to see it, but I'm one person.

DR. KEMPER: Okay. Well, you're the -- you're my boss. So --

(Laughter.)

DR. KEMPER: Well, you know, the

committee. I work at the pleasure of the committee.

CHAIRMAN BOCCHINI: All right. So we have a motion. Let's go ahead and see if there's a second to Coleen's motion to essentially you're asking that we separate the two in terms of a vote, that we can then separate so we could have a vote on one and then a decision on whether to vote on the second or delay that, pending further discussion.

Is that a fair summary of what -- okay. Second of that motion?

DR. BOTKIN: I'm sorry. I need more clarity on which pieces we're separating here. Can we restate what the motion is?

CHAIRMAN BOCCHINI: We're separating this --

DR. BOYLE: So, essentially, what we used to have, the net benefit, is there evidence in terms of net benefit and certainty? So it's that orange part of the -- or whatever color it is of the matrix versus -- so that piece right there.

So, first, we would take, is there essentially -- is there evidence to suggest

significant benefit from screening for condition X, which is what we've been doing all along. And then the second part of that, once we have that, kind of thinking of it as an efficacy-related activity, then we think about the feasibility and readiness issue, which could vary.

Our decisions could vary based on Charlie's example, depression, could vary based on sort of what we think are the drivers in terms of trying to move that forward.

CHAIRMAN BOCCHINI: So, Coleen, maybe I misunderstood what your -- so if we go back to this formal thing? You --

DR. KEMPER: I'm sorry. Which one do you want?

CHAIRMAN BOCCHINI: This one.

DR. KEMPER: Oh, okay.

CHAIRMAN BOCCHINI: You would rather -- you're asking that this be divided into two parts rather than the two votes? Okay. Do you know what I'm saying? So what you're asking is that rather than use this full matrix, that we go back to the

original decision where the net benefit is first determined, and then it comes, if that's agreed upon that the net benefit is good enough to go forward, then the public health? Okay.

And, but we did, I think, discuss that in detail and come forward with the idea that it really needed to be together. So if you want to raise that again, then let's go ahead. That is a motion.

DR. BOYLE: I mean, it can be done in the same meeting.

CHAIRMAN BOCCHINI: Right.

DR. BOYLE: But it's done in a stage process.

CHAIRMAN BOCCHINI: Right. Oh, I see. So, but I mean, essentially, this is what --

DR. KEMPER: Yes, I mean, that's the way I envisioned it. But --

CHAIRMAN BOCCHINI: That's right.

DR. KEMPER: -- I think clarifying that that's how it would be used. But then, ultimately, a letter would be assigned and a number, and then you could look up on those other things. But

there's no way, especially since our 3-D glasses haven't come in, for you to, like, go directly to this.

CHAIRMAN BOCCHINI: But it is presented as a single process, where the net benefit is first looked at. So you would conclude that if the net benefit was not good, then you would not go forward with any feasibility.

All right. So I think since this was posed as a motion, we need to determine if there is a second before we have further discussion about that, now that it's been clarified as to what the motion was.

Is there a second?

(No response.)

CHAIRMAN BOCCHINI: Well, if there is no second, then that goes back to this matrix. And then Steve, and then I think that I saw a hand back up in the -- okay. So, Steve?

DR. MCDONOUGH: Mr. Chairman, I'd like to approve this matrix. I recommend that we approve it for our categorization of nominated conditions.

CHAIRMAN BOCCHINI: Okay. And then do you want to expand that and then say for the second portion to then --

DR. MCDONOUGH: That does not include anything about the second portion, about what we --

CHAIRMAN BOCCHINI: Okay. That would be separate.

DR. MCDONOUGH: About the actual categorization and assigning a letter, I recommend that we approve this.

CHAIRMAN BOCCHINI: Okay. So Steve has -- the motion is that this be approved by the committee, and this does not include a vote on the then matrix subsequently that locks the committee into a decision based on what category this is placed in.

DR. MCDONOUGH: Yes, sir.

CHAIRMAN BOCCHINI: Is there a second to that motion?

DR. BOTKIN: Second.

CHAIRMAN BOCCHINI: Jeff? Okay. All right.

So we will now vote on this. If there's any further discussion? Then we will -- okay.

MS. RACHEL SALZMAN: My name is Rachel Salzman. I just wanted to make the observation -- speaking on behalf of the nominators, I just wanted to comment. I don't think it's reasonable for the nominators to have to do a feasibility and readiness survey as part of that initial two-page nomination submission.

I just wanted to make that comment.

CHAIRMAN BOCCHINI: We agree, and I think this is more towards subsequent to the decision being made to move the nomination -- the nominated condition forward to evidence review, this would be part of any gaps identified at evidence review.

And I think based on your comment and that of prior, Dr. Tarini, it's probably better to remove the nominator from that sentence and just that those gaps be addressed. Some might be the nominator. Some might be States, and so on.

MS. RACHEL SALZMAN: Yes.

CHAIRMAN BOCCHINI: So that's probably

what we'll end up doing.

MS. RACHEL SALZMAN: Thank you.

DR. HOMER: Just a brief comment that in endorsing this, I don't want to preclude that we may choose to divide the Bs. Right now, B1 through 4 is all grouped together, and we may choose to divide them, although I do want to acknowledge that I had not carefully read the definition of "moderate" here.

And "moderate," the way you defined it means directionality could change. And that is, to me, more than moderate. That's a pretty low level of certainty if you're not even sure of the direction.

So some of the language might need clarification to me. I would call that a pretty low level of certainty.

CHAIRMAN BOCCHINI: Okay. So that would certainly play a role in the subsequent decision on how to interpret that, the B.

Okay. Coleen?

DR. BOYLE: Can I ask one more

clarification? Why didn't for the Bs you do the same readiness feasibility --

DR. KEMPER: Right. So the readiness, from an evidence review process, we would still generate that, and you could still vote on that. But the way we envisioned it is that regardless of readiness and feasibility because exactly what Dr. Homer just said about moderate being kind of like moderate minus. That even if people were ready and feasible, there were still important evidentiary gaps that needed to be filled in.

So, but it would be very easy in the future to do exactly as Charlie said, to subdivide things so that you could -- you know, the final matrix. And again, I apologize if I'm overstepping my bounds. But I would imagine on that grid that went out after a decision was made that it would say, B2 or B3 or B4. But just in terms of for decision-making, I just grouped all that stuff together.

DR. KELM: I think in terms of providing feedback on gaps, it may be that it is net benefit

and it might be readiness. So we may want to give somebody a B4 or a B3 to help out with the gaps when they need to go back and do more.

DR. KEMPER: Yes, I agree. That's what I was hoping would come out with this table. But obviously, I didn't explain it well.

CHAIRMAN BOCCHINI: If there's no further comments, we will move to a vote. Oh, I'm sorry. No further comments, we're ready to vote on whether to approve this condition review matrix.

First, are there any abstentions?

(Show of hands.)

CHAIRMAN BOCCHINI: Dr. Wadhwani. Okay. All right.

So we're going to start. Let's go alphabetically the other way.

Okay. Andrea is absent. Cathy?

MS. WICKLUND: Approve.

CHAIRMAN BOCCHINI: Alexis?

DR. THOMPSON: Approve.

CHAIRMAN BOCCHINI: Melissa?

DR. PARISI: Approve.

CHAIRMAN BOCCHINI: Dieter?

DR. MATERN: Approve.

CHAIRMAN BOCCHINI: Steve?

DR. MCDONOUGH: Aye.

CHAIRMAN BOCCHINI: Chris DeGraw?

DR. DEGRAW: Aye.

CHAIRMAN BOCCHINI: Fred?

DR. LOREY: Aye.

CHAIRMAN BOCCHINI: Kellie?

DR. KELM: Approve.

CHAIRMAN BOCCHINI: Chuck?

DR. BOTKIN: Approve.

CHAIRMAN BOCCHINI: Coleen?

DR. BOYLE: Okay.

(Laughter.)

DR. KEMPER: That was definitely moderate approval. Where is that on the --

CHAIRMAN BOCCHINI: It's either an A3 or a B1. Is that right?

Jeff?

DR. BOTKIN: I thought I already voted. Yes. Approve.

CHAIRMAN BOCCHINI: Okay. And I approve.

DR. HOMER: I approve, too.

(Laughter.)

DR. COPELAND: He called you Chuck, and you said yes. At least that's what I heard, but I could be wrong.

So we will --

CHAIRMAN BOCCHINI: Sorry about that.

DR. COPELAND: We will arrange to have a discussion about where things fall in terms of addition to the RUSP at a later point in time.

CHAIRMAN BOCCHINI: Okay. Alex, thank you very much.

All right. Next on the agenda is a discussion of adrenoleukodystrophy, the Nomination and Prioritization Committee report. Dr. Lorey will provide the report from the committee.

Committee members are aware we received this condition nomination. It was reviewed by the committee, and Dr. Lorey will present the report.

DR. LOREY: Thank you. I didn't realize I was going to have to give this right after the

preceding discussion.

And first, I wanted to thank all the members of the ALD community who came today and gave their testimonials. We appreciate the input.

These slides are a summary of the Nomination and Prioritization Committee review, and they're in a designated template for this review process.

So, condition information. Type of disorder is adrenal insufficiency and neurodegeneration. There are treatment strategies available. Hormone replacement therapy for adrenal insufficiency. Hematopoietic stem cell transplant for the demyelination. You heard about this from Dr. Moser and others earlier.

The nominator is Dr. Charlie Peters, and there are a number of ALD advocate organizations, as you can see, supporting this nomination.

Key question number one. Are there prospective pilot data in the U.S. or internationally based for a population-based assessment available for this disorder?

Yes, there are. I do want to have a couple disclaimers here in the beginning because there's been a lot of discussion about the definition of the word "pilot." And I've used sort of a -- just for the sake of consistency, I've used that word in all three of these cases, though they may not fit the narrow definition of "pilot," which would include prospective studies following positives through diagnosis.

You've already heard about a couple of these from Dr. Moser. Her first study probably would not be called a pilot study, but this was the initial testing process where she had not only controls, but dried blood spots from known cases from California and Michigan.

There were a total of 17, 16 identified correctly. But I will say she stated in her paper they believe the one case to be a misidentified case that actually wasn't the case rather than a miscase. It wasn't the correct sample. Excuse me.

Pilot number two does fit more closely the definition of a pilot because it was a prospective

study -- she mentioned that this morning as well -- of 5,000 samples. They were being prospective. It fits the definition.

However, only being 5,000, there were no initial positives or true positives or false negatives, for that matter. So we don't have all the information there.

Currently, the biggest study is underway at Mayo under Dr. Matern. And it doesn't fit the -- it's more a hybrid because it involves two large parts. One, the testing of known cases from dried blood spots, and then 100,000 prospective specimens coming from our lab in California. And in subsequent slides, you'll see a little bit more about that.

Does the screening test have established analytic validation? Some published by Dr. Moser and some are still underway in the Mayo study but not published yet. But we do know early onset cases are readily detected in all of the current studies or past studies.

Is there a widely available confirmatory

test/diagnostic process FDA approved? Yes, there is. Plasma testing at Johns Hopkins and four other labs in the U.S., and Dr. Matern provided this Web site URL for all of those places.

And MRI screening semi-annually with diagnosis by specific findings with cerebral inflammation in 80 percent of affected boys. So there's a lot of monitoring going on now.

Is the condition medically serious? Yes.

The case definition in this spectrum of the disorder is well described to help predict this phenotypic range of those children who will be identified based on population screening? For the most part, yes.

There are attenuated forms, adult onset forms. We don't have as much information as far as testing of newborn spots on those. There is some -- and this comes directly from the nominators' bullet two, there are some uncertain genotype-phenotype correlates. Most of the cases up until now have been determined by clinical identification, and the estimated combined male and female frequency is

about 1 in 17,000.

Neurologic problems are found in about half of the female carriers, and half of the diagnosed males have late onset forms. Some could change with universal screening, but that's what we know now.

How to address the clinical needs of these folks are not addressed in the nomination. Treatment, efficacy is uncertain for those with later onset forms.

Information 3. Characteristics of the screening test for the newborn screening system. Among other aspects, a low rate of false negatives.

The data to date has been pretty consistent, and both of the Moser studies were done by tandem mass spectrometry without chromatic separation, and multiplexing with acylcarnitines is possible.

And the Mayo study, also done with tandem mass spectrometry, along with six LSD enzyme assays in the same multiplexed system.

Some of the potential harms of screening

and testing. Patients affected with peroxisomal biogenesis disorders and 70 to 85 percent of ALD heterozygous females will be detected by this assay.

Post analytical tools based on the R4S model are available to discriminate these cases from females affected with other peroxisomal disorders. And I verified that with Dr. Rinaldo yesterday to make sure that was true.

Okay. Some of the information from the Mayo study, and thank you, Dr. Matern, for providing some updates. Normal values were established analyzing 340 anonymized newborn screening blood spots.

To date, they've received 30 ALD newborn spots, 16 from Kennedy Krieger Institute and another 14 from the California Department of Public Health. Two additional peroxisomal spots were received under this IRB study.

To date, 6 ALD carriers, known carriers newborn spots have been received from California, and 11 additional to date -- this is a continuing study -- family members of unknown genotype, meaning

they didn't have genetic testing.

And then, additional 12 newborn spots for Kennedy Krieger and 12 carrier non-newborn spots from Kennedy Krieger. And then, as I mentioned, the 100,000 prospective spots from California, and we're at about 42,000 at this point.

This slide was summary of the Mayo study to date was provided by Dr. Matern. Thank you very much. At about 42,000 samples, the first-tier MS/MS analysis gave us a 1.2 percent positive rate with 384 females and 159 males.

Moving on to the second tier, however, takes us way down to a positive rate of 0.03 percent. And currently, that is 7 females and 5 males, which are pending genotyping.

If the spectrum of disease is broad, those who are most likely to benefit from treatment are identifiable, especially if treatment is onerous or risky. Yes, the early onset cases are easily identifiable in stored newborn spots.

There's less clarity about adult onset. And as I said, we don't have any newborn spots from

them at this point.

Reports have described the initial success of stem cell transplantation for a patient with long-term beneficial effects of that transplantation in a large international experience. With monitoring, timely and effective stem cell transplantation can be achieved. A 95 percent 5-year survival with excellent clinical outcomes, compared to 54 percent survival for a similar group not treated with stem cell transplantation.

Of note, boys in the untreated group progress to a vegetative state and death. Survival for transplanted patients is 92 percent for boys with early stage brain disease compared with 45 percent at 5 years for patients with late-stage disease.

Identification of ALD can lead to timely diagnosis of adrenal insufficiency and initiation of hormone replacement therapy. A metabolic crisis due to unrecognized and consequently untreated adrenal insufficiency can be fatal or result in significant morbidity with long-term sequelae, including

profound rapid neurological deterioration in boys with ALD. And I think some of the speakers this morning presented that probably more clearly than I did.

Defined treatment protocols, FDA approved drugs, and treatment are all available. These are requirements, these first headings. Maintenance and stress dosing adrenal hormone replacement therapy is the standard of care for the adrenal insufficiency, including that associated with ALD.

Stem cell transplantation is the only effective long-term treatment for ALD. However, to achieve optimal survival and clinical outcomes, this transplantation must occur prior to manifestation of symptoms. Gene therapy, experimental treatment has been shown to be safe and efficacious.

Urgency. It is imperative to implement by 3 months -- these are from the nominators, by the way. It is imperative to implement by 3 months the following. Adrenocortical function testing to detect adrenal insufficiency. And by 3 years, serial neuroimaging to detect early evidence of

demyelination.

So we had a discussion at the end of this call. These first few items, which are requirements, have been established -- the case definition, the screening and diagnostic protocol, the treatment protocols.

Some pilot testing, with a caveat of what a pilot is, has been done or is underway. What is missing is a pilot with prospective studies all the way through diagnosis with patient follow-up.

There is the appeal of multiplexed testing, that you can do this along with the LSDs in actually several other disorders as well.

Although the workgroup noted several positives aspects in most of the areas of consideration, the review should not move forward until the largest and latest pilot study, this green test, is completed and data are published or at least further along.

Researchers at the Mayo biochemical genetics lab are willing to provide updated results to the committee as they are obtained. We recommend

the nominators resubmit the nomination at this time.

So our recommendation is to not move forward at this time, mainly because we don't have that very important piece of a prospective study following the patients through to diagnosis and knowing what else we're going to find.

Now what we've seen so far is a very low false positive rate, maybe even zero. But we won't know that until we actually do prospective studies. So that is the committee's recommendation.

CHAIRMAN BOCCHINI: Fred, thank you very much for a very clear presentation of the issues and summary of what the Nominating Committee reviewed and discussed.

It is now open to the committee for discussion. Steve?

DR. MCDONOUGH: What is the cost of the test?

CHAIRMAN BOCCHINI: Fred, I don't think we have that data. The cost of the test? We do?

DR. LOREY: I don't have that. Dieter, do you have --

DR. RAYMOND: Well, we can say that it's $2 a sample.

DR. LOREY: Two dollars a sample?

DR. RAYMOND: Yes.

DR. MATERN: Do you want me to comment on this, too?

CHAIRMAN BOCCHINI: Sure. Yes.

DR. MATERN: That's probably in the same ballpark. And also there's a difference if you do it as a standalone test. So if you only look for the LPCs, it's $2. If you add other conditions in the same analysis, then, of course, it becomes overall cheaper, I would think.

CHAIRMAN BOCCHINI: Let's see. Well, first, Jeff, did you have a comment, question?

DR. BOTKIN: Two questions. Are there any racial or ethnic aspects to the condition prevalencies? And then, secondly, for a child who is diagnosed in the newborn period, can you tell whether that child is severe newborn onset versus adult onset?

DR. LOREY: I'm certainly not the expert

here, but I don't believe we've obtained any newborn spots of late onset patients. So I don't know if somebody from the audience may have?

DR. RAYMOND: So the newborn -- the disorder is a very broad disorder. It results from a defect in the ABCD1 gene. When that defect occurs, you have an elevation of very long chain fatty acids that affects a peroxisomal transporter that results in an abnormality of beta -- peroxisomal beta oxidation.

Within the same family, there is no genotype-phenotype correlation. So over half of our families, one child -- one boy will have the childhood form, and the other brother will have the adult form of the condition. And we think that there may be some other second hit or modifiers. We do not completely understand that at this moment.

I want to emphasize, though, that those newborn blood spots were from a heterogeneous group. They were from individuals who both went on to develop childhood cerebral disease as well as the -- as well as individuals we suspect will develop adult

forms. It is not important to that aspect.

What is important, though, is to recognize that still 90 percent of those individuals are going to develop adrenal insufficiency, some in childhood. Secondly, you cannot predict, looking at a newborn, who is going to develop childhood disease. So that the monitoring has to occur to all of those individuals at risk.

However, that's extraordinarily important because you cannot predict. And so, we have to, when we identify someone who is a newborn, go forward as that child is at risk for childhood cerebral disease. And that's a third to 35, 40 percent of that population.

What was the second question? I don't --

DR. BOTKIN: Racial?

DR. RAYMOND: Racial and ethnic. No, this affects all racial and ethnic groups. We have -- I have African Americans. I have Caucasians. I have people from Asia, New Zealand. Maori Polynesians. We have it all.

And to also emphasize that we have -- it's

not -- that's not all that surprising. This is an X-linked disorder. So we have a significantly high new mutation rate. Five to 7 percent of our cases you cannot find another individual.

So that is another reason why we didn't just latch onto this. If we could identify based upon screening families extensively, that would have been the way to go. But new individuals come to our attention all the time.

DR. LOREY: I have one question and one comment. So are you saying then that a patient who you know later to have late onset would have elevated C26.0?

DR. RAYMOND: Absolutely. Absolutely.

DR. LOREY: Okay. And the one thing I forgot to mention is reserve cord blinded studies that we send, and all of the carriers have been correctly identified as well.

DR. HOMER: I guess, again, the question I'd have is more one of process, which is what's the bar for sending -- we're not voting now on putting something on the RUSP. We're voting for whether to

do an evidence review.

And again, my sense, reviewing the slides -- and I apologize I was unable to make the subcommittee meeting -- is there's certainly a strong suggestion and many of the criteria are met and the literature is evolving. So personally, it feels to me that a more detailed evidence review would be appropriate, and I'm not clear where our bar is.

Related to that is our ability to include studies in progress, when and how whether the committee has opined previously about whether something actually needs to be formally through the peer review process. Or if investigators, as in this case, are willing to share their data with us, be transparent about their methods, whether we're willing to consider that information?

CHAIRMAN BOCCHINI: Sara, you want to talk to this?

DR. COPELAND: The barrier is at the committee's discretion, but the most important one being that there has been a mechanism to start doing

this on a population-based screening. But the bar is at the discretion of the committee.

CHAIRMAN BOCCHINI: But I think that was the key issue was that the major pilot study, the prospective study is underway. But the data is not available yet at the outcome of that study. And so, that was the primary reason for the decision, as Fred pointed out.

So let's go to Dieter, and then we'll go around the committee first, and then we'll come to --

DR. MATERN: I also wasn't on that phone conference call. And again, if that went forward, we'll be happy to share our data with the review group and try to publish it as soon as we can. But really, the study won't be done until end of September next year, especially if California sends more samples.

The other thing, point I wanted to make, and the colleagues from Kennedy Krieger might comment on that, too, is that we are talking about ALD, but we're screening, looking at

lysophosphatidylcholines, which are not a specific marker for ALD, but you pick up other peroxisomal disorders as well. Which, in itself, I don't think is a problem, but that's maybe my personal perspective that because some of the conditions we cannot do anything about, such as Zellweger syndrome.

So if this goes forward or whenever it goes forward, one has to consider that there might be primary and secondary targets here that one is dealing with. I think that's all I wanted to say.

CHAIRMAN BOCCHINI: Thank you.

Other committee? Okay. Dr. Lavenstein?

DR. LAVENSTEIN: I just wanted to make a sort of clinical and neurologic evaluation point on your slide about the neuroimaging, Dr. Lorey. As the technology has gotten better, we've gotten faster at the ability to pick these cases up.

So as the resolution of MRI scanning gets better, you can see correlations between disease and progression of disease. And as many know, for adrenomyloneuropathy, for example, we thought it was

a spinal cord disease. But if you do high resolution diffusion tensor imaging, you actually see brain involvement, even though you will not see it on conventional MRI scanning.

Similarly, there have been papers recently I think in the literature that have been able to look at effectiveness of stem cell transplant in patients using diffusion tensor imaging versus merely using standard 1.5 tesla MRI scanning.

So one would think about marrying some of the high-technology tools become available as you think about moving beyond the screening procedure to monitor the success of various therapeutic outcomes, but also to identify earlier those patients in whom you see changes well before you see it on conventional MRI.

And any centers that are really involved in this are going to have high-end neuroradiology that could do diffusion tensor imaging. So I would suggest we look at that literature because that's really moving forward fast.

CHAIRMAN BOCCHINI: Thank you. Yes?

DR. GETCHELL: I'm just curious to know about the difference between the first-tier and the second-tier test. And I don't know if that's a question for Dieter or Fred.

DR. MATERN: The way that we do it is we have a flow injection analysis tandem mass spec method similar to the amino acids and acylcarnitines for the LPCs. That means there is no liquid chromatography step in front.

The second-tier assay is basically also -- is the original LC/MS/MS assay basically, as the Kennedy Krieger group described it. And the way we do it, we reinject the extracted and prepared blood spot sample into an LC/MS/MS system. So you do not need to do another punch. You just reinject whenever you find an abnormality, and then it usually comes back normal.

And the initial false positive rate, as it was, on the slide of 1.3 percent or whatever, is going to go down as we modify our cutoffs as we get the molecular data back and can adjust those accordingly.

DR. GETCHELL: And that requires a single run?

DR. MATERN: If you only want to do the LPCs, yes. That's currently a single run.

Now as Kennedy Krieger mentioned, they have developed a method where you combine the LPCs with the acylcarnitines, which personally I don't know if that gets us very much, since we run the acylcarnitines with the amino acids very successfully. And I don't see a good reason to take those apart now.

We do the LPCs along with six LSDs that are being discussed, apparently also to be included and are being included in some States. So you could basically get the LPCs with the LSDs that you might want to screen for anyway.

DR. PARISI: And on that second tier, did that also pick up the Zellwegers and the other secondary conditions? So after the second tier of testing, you still have those included?

DR. MATERN: Yes, we basically look for the same analytes, just with a slightly better

method. So the differential diagnosis will be the same.

DR. RAYMOND: So in the discussion about picking up peroxisomal biogenesis disorders and other single enzyme disorders of beta oxidation, yes, we will pick those up. However, that is not necessarily a bad thing.

It will allow for earlier diagnosis, and in fact, the largest family support group, the Global Foundation for Peroxisomal Disorders, which I participate, is also in support of newborn screening. But it is not necessarily the primary reason we're trying to go forward.

CHAIRMAN BOCCHINI: Thank you. Jeff?

DR. BOTKIN: Is it the group's assessment at this point that the current pilot study that's being conducted will provide adequate evidence on the performance of this test in a population screening environment? In other words, when this pilot is done, is that going to provide the evidence that the committee might need to make a final decision about this depending on what the results

are?

DR. MATERN: The idea of the whole study is to provide all the information about the efficiency and effectiveness of the test. So the answer, I guess, is yes.

We are running this test. We receive about 1,000 specimens every week from California, and we run those basically over the following week. So it's a real live screening scenario.

So I think it certainly fits into a screening program, and that has been shown by Kennedy Krieger, of course, in work with Maryland. And I believe they ran it in the Maryland laboratory with their existing equipment.

And I will abstain from voting.

CHAIRMAN BOCCHINI: From the audience, if you'll identify yourself?

MS. AMBER SALZMAN: Yes. My name is Amber Salzman.

I greatly appreciate the need for a prospective identification. But just logistically, obviously, we feel very strongly that the sooner

this test is implemented, the more babies that will be saved. So there's a timing here in terms of getting into the queue of evidence review.

And while the Mayo study will be done by next September, there are spots that are currently, as was mentioned in the data, identified as positive. And there is confirmatory test available right now. I mean, Kennedy Krieger has mentioned that's available.

So it could be done during the evidence review very -- in a prospective way to do the confirmatory testing on those that have already been identified. And then by the conclusion of the evidence review, by that time, the 100,000 that Mayo is currently testing would be done.

So just, respectfully, another reason to push forward and get in the queue so that more lives will be saved.

CHAIRMAN BOCCHINI: Thank you.

Steve, and then we'll go to Nancy.

DR. MCDONOUGH: Mr. Chairman, there's no deadline if we make a recommendation on a condition

to go for evidence review to have that evidence review come back at the next meeting, is there? I mean, it can take a year or a year and a half to come back, depending on where the evidence is?

CHAIRMAN BOCCHINI: Yes, we have two conditions already in the queue that are being reviewed. You're going to hear about one in a few minutes. So, no.

DR. GREEN: Okay, thank you. Nancy Green, Columbia University.

Fred, thank you for a great presentation.

And being part of the Nomination Committee, Workgroup, rather, this has been an interesting vetting process. But one thing that sort of didn't come out in our discussion and in the literature that was submitted as part of the nomination process that when we think about Alex's matrix and, you know, another sort of ripple, and that is I'm confused about the specificity of the screening.

So as Fred presented, there's a spectrum of male and females that are affected or are

carriers who may have long-term physical impairments from the condition. So the proportion of people who are screened for ALD who are actually need urgent -- and I know that's a broad definition, but care. Implementation of care. So what's that proportion, number one?

And number two, then what's the full range of disorders that are also picked up or suggested by screening these other peroxisomal disorders?

So I just think that -- I mean, I've not understood that range in particular. And so, as we're talking about what means a pilot, I think the committee should consider or be informed about what other -- I forget the term. It's not off target, but additional disorders would be suggested.

It's not entirely incidental, but anyway. So I'm not sure that so that sort of whole package has been clearly described, at least in my mind. I don't know, Fred, if you have a better sense of that?

DR. LOREY: I don't, but I think we'll know a little more when the molecular studies have

been completed because we do have a number of positives.

DR. RAYMOND: Do you want me to address that?

DR. LOREY: Is that right, Dieter?

DR. RAYMOND: Would you like me to address that?

DR. LOREY: Sure. Please.

DR. RAYMOND: Yes. So the testing is pretty much a test of a biochemical abnormality of a peroxisomal beta oxidation. And so, there are -- the most common disorder of peroxisomal beta oxidation is X-linked adrenoleukodystrophy, which also has a spectrum which could use -- without a PowerPoint slide, it makes it even more confusing.

Let's talk about X-linked adrenoleukodystrophy for one second. X-linked adrenoleukodystrophy is a disorder that does have a spectrum within it. However, once again, while it affects every tissue of the body, 90 percent of individuals will develop in childhood of males' adrenal insufficiency.

Of that 90 percent, of those males, 35 percent will probably develop childhood cerebral disease. Sixty-five percent will go on to develop an adult form of this condition, but they are still at risk for developing adrenal insufficiency in childhood.

Women who are carriers typically will develop symptoms in adulthood, and we would not be proposing screening just based upon screening for women who are going to develop the disease in adulthood. They don't typically develop adrenal insufficiency also.

The other secondary disorders or other disorders that relate to this fall into two broad groups, peroxisomal assembly disorders, sometimes referred to as Zellweger syndrome or Zellweger spectrum disorder, which are highly variable but also can have adrenal insufficiency, as well as single enzyme disorders because that is naturally a pathway, and we're only measuring sort of the analyte.

And so, it's acylcholyoxidase and

bifunctional enzyme deficiencies which are usually significant diseases, but also can present with adrenal insufficiency.

CHAIRMAN BOCCHINI: So, in the interest of time, I'm going to limit to two more comment -- well, three. One, two, and then the microphone. So, Beth first.

DR. TARINI: I have a more pointed question on the lines of Dr. Green. How are we going to decide which babies get stem cell transplant? In particular, A, what is the plan, or will it be addressed if we don't know now, for differentiating those babies with ALD versus other conditions?

And of those babies with ALD, the ones who have adrenal insufficiency, which was one major complication, and then will be at risk at some point to develop cerebral pathology, what is the plan for transplant on those babies?

DR. RAYMOND: We don't transplant everyone right in the newborn period. We monitor them with MRI, and that's what we're presently doing with

individuals we identify.

They get monitored with MRI at about 6 to 12 months periodically ongoing, right through the period of high risk.

DR. TARINI: Thank you.

CHAIRMAN BOCCHINI: Carol?

DR. GREENE: And speaking for -- without having had a chance to poll my membership, but speaking for the SIMD as a representative random clinical geneticist who sees kids with these disorders, I am perfectly and completely comfortable that if I got a phone call from a newborn screening lab, that I have enough understanding of the variable expression and the clinical monitoring that I would feel perfectly comfortable sitting with a family and saying I know what to do.

I know how to not over treat, and I know how to monitor to make sure I treat the baby. And I think you would hear that from pretty much all my colleagues, very comfortable. I'm also very comfortable that the other conditions that are picked up are either incredibly more severe or, for

those that are mild that could be confusing, incredibly rare.

And we do understand the phenotype and the natural history of these diseases very well, and I'd be very comfortable getting a call from a State lab.

CHAIRMAN BOCCHINI: Thank you.

Last comment, microphone?

DR. OSTRANDER: Hi, Dr. Ostrander, NYMAC, New York City Academy of Family Physicians.

This may be simplistic, but it does strike me from listening to this that, indeed, there is an intervention that 100 percent of screen positive males would have -- make a huge difference over the short haul, and that is monitoring for adrenal insufficiency. What I didn't hear is what that protocol and routine is. But I'm sure you've got one.

But specifically, that seems to me that that's a target. It's an intervention. It's not a treatment. But they do have a targeted intervention that has great potential for benefit, low cost, and should be implemented on everyone, not just people

with certain spectrum of the disease.

So, to me, that speaks -- makes this a more qualified nomination, regardless of the neurological manifestation or the adult manifestations of the disease.

Thanks.

CHAIRMAN BOCCHINI: Thank you.

All right. We have the -- we've had a very good discussion. We have the recommendations of the Nomination and Prioritization Committee. We need a motion to accept the recommendation of the committee so we could pose it for a vote.

Do we have a --

Doctor, okay. So. So the --

Jeff, then your vote -- your motion is to accept the advice of the Nomination and Prioritization Committee to not bring this forward for evidence review at the present time and ask that upon completion or that we be made aware on an ongoing basis of the pilot prospective study so that once completed we can reevaluate the nomination.

Is that fair?

DR. BOTKIN: Yes, that's fair. And if I could add the comment, I see it more as a process issue at this point. It sounds like the committee is likely to move forward to an evidence review at some point.

And so, it's not clear to me that taking this vote today delays that overall process because we're still waiting for data. I don't think we want to set up the review committee to do a lot of work and then say there's nothing to vote on because the evidence isn't in yet.

So my support for this is simply a process kind of question to say support the committee -- support the group to say let's do the review when it's likely to have the data in hand to make a committee decision.

CHAIRMAN BOCCHINI: Thank you.

Is there a second?

DR. THOMPSON: Second.

CHAIRMAN BOCCHINI: Alexis? All right.

It's been nominated and seconded. So now we will have a vote. I'm going to start in the

middle this time.

First ask if there's any abstentions?

DR. MATERN: Here.

CHAIRMAN BOCCHINI: Dieter and Dr. Wadhwani. Okay. All right.

Good. You're ahead of me.

Okay. Let's start with Kellie Kelm?

DR. KELM: Approve.

CHAIRMAN BOCCHINI: Fred Lorey?

DR. LOREY: Approve.

CHAIRMAN BOCCHINI: Chris DeGraw?

DR. DEGRAW: Approve.

CHAIRMAN BOCCHINI: Steve McDonough?

DR. MCDONOUGH: Aye.

CHAIRMAN BOCCHINI: Melissa Parisi?

DR. PARISI: Aye.

CHAIRMAN BOCCHINI: Alexis Thompson?

DR. THOMPSON: Aye.

CHAIRMAN BOCCHINI: Cathy Wicklund?

MS. WICKLUND: Approve.

CHAIRMAN BOCCHINI: I approve.

Dr. Botkin?

DR. BOTKIN: Approve.

CHAIRMAN BOCCHINI: Coleen Boyle?

DR. BOYLE: Aye. Yes.

CHAIRMAN BOCCHINI: And Charles Homer? We're going to give you a chance to vote this time.

DR. HOMER: Nay.

CHAIRMAN BOCCHINI: All right. That completes the vote. The decision is made to not move forward.

But we certainly want to thank the group for bringing this nomination. It's very clear that you have met a number of the standards of the Nomination and Prioritization Committee, and we look forward to continuing to receive additional information about the pilot study so that we can potentially move this forward to the next step.

Thank you very much.

All right. Next on the agenda is an update on the Pompe nomination. Dr. Kemper is going to make his way back up here from way in the back of the room.

DR. KEMPER: What I'd like to do in the

time that I have is just to provide everyone with a quick update with where we are. It's my hope that we have the review, including the public health impact evaluation, ready for the January meeting.

Oh, you can't hear me? Can you hear me now?

January meeting is when we hope to have all the pieces ready for a vote on the matrix, which I will not discuss any further.

But let me go ahead and thank the group that we are working with, including those members from the Advisory Committee who are helping us wrestle through some of the complicated issues. And there's at least a couple of things I'd like to bring out to the group for their advice as well.

So, to update everyone where we are, we've completed two technical expert panel teleconferences. And this is a process that we began with the CCHD screening review, and I'm going to talk about what we've learned in it. But that process of talking to the experts up front has really proven to be invaluable.

We've developed a scope of review, including the case definition, the newborn screening and diagnostic procedures, the key questions, and have identified the key sources of data. We've drafted the preliminary evidence review protocol, which we're actually going ahead and working on. And we've completed the initial literature search.

So that's the comprehensive search I can talk about. If anybody wants to actually see the whole search, back in my briefcase, I have a huge folder.

So let me talk first about the technical expert panels calls that we've had. You can see the experts that we've had. They really represent the broad gamut of expertise from clinicians who are in the trenches managing individuals with Pompe disease through genetic epidemiologists and researchers active in the field. And again, I'd like to publicly acknowledge how helpful these experts were in helping us understand what the salient issues are.

So the first technical expert panel call

was really focused on developing a case definition, which, again, I'll show you in a few minutes, to refine the key questions, and to identify sources of information that we might not otherwise be aware of.

The second technical expert panel call really built on the things that we learned during the first call, but really focused on issues of what would be expected standard of care in terms of screening and how one should establish the diagnosis, to review the decision-making practice around when treatment should be initiated, and then to describe the process and timing of immune therapy relative to the started enzyme replacement therapy.

If you remember from our discussion earlier, one of the challenges about treating Pompe disease is that there are some individuals who are so-called CRIM negative. They don't produce any of the enzyme themselves. And so, when they get enzyme replacement therapy, they're at risk to develop antibodies which would then decrease the effectiveness of the therapy.

So this is a slide, unfortunately, Anne

Comeau couldn't be here today. But she really has helped put this together in terms of understanding the approach to screening. And it's not my goal to go through all these different steps, but just to make you aware of that there are these variations even beyond what particular method is used to measure the enzyme.

But in terms of how you deal with making -- doing the screening based on one dried blood spot or two dried blood spots. So in this figure here, you can see that, for example, if the first dried blood spot has normal levels of the enzyme, then you're done and no further action needs to be taken.

But the issues then become whether or not if it's low or if the enzyme level is absent. And so, typically, what's done is the same dried blood spot would be evaluated again to measure the enzyme level. And then based on that, there would be a repeat testing or more urgent follow-up for diagnosis.

And there's any number of different ways to do this and to set the levels, and that's one of

the things that we're going to have to clarify well for this group, just so that when we talk about things like predictive value, it makes sense about what we're talking about. Again, this is sort of a similar issue that we've faced before.

In terms of treatment initiated -- treatment initiation, it's clear from the experts in the field and those who manage patients that treatment can go ahead and be initiated for those with low enzyme levels pending genetic confirmation because, of course, that genetic confirmation takes some time to come out.

The other thing that I learned through the process of these calls is that genotyping can inform whether or not the individual is going to be CRIM positive or CRIM negative, which, as I said before, can affect treatment response.

So one of the questions that I had for the group was if the current thinking is that you have to hold off on beginning enzyme replacement until you can verify CRIM status or whether or not you can go ahead and begin therapy and then use

immunomodulation once the CRIM status is identified?

Again, this is really emerging work, and a lot of it's not in the literature right now. But it was the general consensus of the people on the call that therapy can begin early with immunomodulation coming later.

The other thing that we learned that I hadn't seen in the material that I've reviewed thus far is that there are some CRIM positive individuals that can develop antibodies, and they would require immunomodulation. Now I can't tell you how often that happens, but I think that's something that we're going to need to explore and also understand how that impacts on the effectiveness of treatment.

One of the real challenges is that if you remember when we first looked at Pompe disease, this was really in the Pliocene era before we had the formal process for evidence review. And one of the things that we did not look at, and this was an explicit decision, was the so-called late onset or the later onset individuals with Pompe disease.

And it's pretty clear that that's an

important group to understand. It's important to understand what proportion of individuals that will be identified through screening will turn out to have later onset disease and what's the benefit of treatment and how do you decide when to treat this?

One of the things that I've learned from at least the experts that we've spoken to so far is that there's really no standard agreed-upon protocol for the management of those with suspected later onset disease. So how frequently do you follow them into the specialty clinic or the general clinic? What sort of things do you follow them? How do you determine when treatment should begin?

And of course, like all the other rare conditions that we think about, it's not surprising that those protocols haven't emerged because that's a population of individuals that are just now being identified. But it does increase the challenge that we have in terms of understanding what's the impact of having later onset disease.

And that's a question I'm going to pose to the group once I'm done with this presentation.

So, again, in terms of the scope of review, we've identified a case definition that we're using, the screening and diagnostic procedures, key questions, and have identified other relevant sources of information that we're going to be looking at.

I don't want to spend a lot of time on the case definition. I guess we've discussed it before, and it hasn't really changed.

But there's the infantile form, which can be subdivided into the classic form, which is rapidly progressive, characterized by cardiomegaly, hepatomegaly, weakness, hypotonia, and death usually in the first year of life. Versus the nonclassic, which is slower progressive, has less severe cardiomyopathy than the classic form.

And there's also what in the original review we referred to as late onset, but I'm referring to as "later onset." I think that's in alignment with what other experts in the field use, and that's to emphasize the fact that it's a spectrum. So it's not like there's this clear

dividing line between the different forms.

So the later onset form exists on a wide spectrum and can be broken down. There's a childhood form, a juvenile form, a muscular variant. These usually present after infancy, and they typically don't include cardiomyopathy.

And then there's an adult onset form that's associated with a slowly progressive myopathy predominantly involving skeletal and respiratory muscles or noncardiac muscle. And it can begin to present anywhere really between the second and sixth decade of life. So there's a broad spectrum in there.

So to anticipate a question that you might ask me right now is what do we know about the epidemiology in terms of what percentage of people fall into each category? And I can't answer that question with confidence right now, but it's clearly something that we need to talk about.

I'd like to just talk to you briefly about the key questions that we're going to be abstracting the data into. There's the first one, what factors

are present -- what factors present in newborns affect the age of onset of the disease course of individuals with Pompe disease? What's the direct evidence from the pilot newborn screening studies that screening for Pompe disease reduces morbidity or mortality, and how does this vary by the form of Pompe disease or CRIM status?

What's the analytic validity and clinical utility of the various screening approaches used in the pilot studies to diagnose Pompe disease and distinguish these forms? What diagnostic tests are available, and can diagnostic testing differentiate between the forms of Pompe? That is age of onset in a timely manner. What are the most important intermediate outcomes related to the treatment of Pompe disease?

Does early initiation of enzyme replacement make a difference in these intermediate health outcomes when the condition is caught earlier through screening? Do follow-up protocols exist for the management of Pompe disease that does not require immediate initiation of enzyme replacement

therapy? I guess, oops, I kind of answered that one already.

What's known about the effectiveness of follow-up protocols? And are there factors that modify the affected treatment, for example, CRIM status? And how big of a deal is that, and are there other things other than CRIM status that we should be thinking about?

What are the most important health outcomes related to the treatment of Pompe disease? And I won't read through all this. But basically, what are the factors that are involved in that?

And then, finally, how strong is the association between intermediate outcomes of improvement for Pompe disease and the long term for the significant health outcomes? You remember this was all from that analytic framework.

What are the harms of false positive screening to the individual and the family? And what are the harms associated with treatment, and has this varied by form, et cetera?

Oops, I'm sorry. So we've conducted our

literature search, looking at both PubMed and EMBASE using a variety of match terms and their associated key words. And you can see that there are like 2,000 or so articles. Obviously, not all of these are going to be included.

But there was actually a fair amount more there than I would have guessed, and I actually have a slide coming up on it. But really, a lot of it is related to the late onset disease, which kind of creates a challenge in terms of telling a story that's important to this group.

These are standard inclusion and exclusion criteria for the studies. And again, we're having two independent reviewers look at all the abstracts, and if we can't figure out if something should be included or not, we have a third reviewer looking at things. Again, this is all of our standard approach.

This is what I wanted to talk about before, which is just our first pass through at the literature. There's a lot written on the immunomodulation, and certainly that's a very hot

area of active research. So I think that with some confidence, I'm going to be able to tell a good story about the CRIM status and the degree to which that's a big deal or not a big deal.

But there's a ton of stuff out there on the later onset Pompe disease. Again, we like completely excluded that stuff from before. I'd appreciate guidance from this group in terms of level of interest or how important these issues are, especially because it's still an emerging field, and even the guidelines for follow-up are still under debate. Again, a lot of the later onset stuff is from case studies, which we do include.

In terms of Grey literature, we've cast our usual broad net looking for anything that's out there. I think the one thing that's going to be helpful is the Pompe Disease Registry, and I hope that we'll be able to tell a nice story out of that.

And then, here we go. These are other relevant sources of information. Dr. Kishnani, who is the nominator, does have also a database of patients based on their CRIM status and other

associated factors. And Dr. Bodamer has some further information for us on the Austrian study.

So I think there's going to be a lot of stuff here about the early screening and early treatment, and it's just hard to know how much effort to put onto these issues related to the later onset disease.

We are going to, as we described before in our methods post the protocol for our review process, as part of the transparency issue, we're in the process of going through all these articles and abstracting them. We will revisit as we go along with key informants and do interviews just to make sure that we understand things.

There's the Grey literature analysis. Dr. Prosser at the University of Michigan is now working on the net benefit modeling and preparing a decision analytic framework and so forth. So that as we generate the data, she can put that into there, and she'll also be working with us around issues of key informant interviews for areas of uncertainty.

Again, this is no different than how we

worked with the screening for chronic bilirubin encephalopathy. I think that that was a great model for that.

And then we are just now beginning to start the process of working with APHL and looking at issues related to public health readiness and feasibility. But I guess I'll just kind of leave it there.

So I just wanted to open the floor for questions about sort of our general process, but also look to you for guidance around how much of the story around later onset disease would be helpful to you in the decision-making process. That will just help us. Maybe that's not a well-formed enough question.

So, with that, my nebulous thing, I'll turn it over to Dr. Bocchini.

CHAIRMAN BOCCHINI: Alex, thank you. I think it does give you a good feel for the complexity of the issues as they are -- as you go through the evidence review.

So we have a couple of minutes for some

quick questions. So, Steve?

DR. MCDONOUGH: Will Pompe be the first condition that will be used in the new matrix? And what timetable do you think that it will be coming back to the committee?

DR. KEMPER: Yes. And January, barring any foreseen crisis, which I will inform the Advisory Committee of.

DR. HOMER: I guess in terms of the late onset, now I can ask questions because I know nothing clinically about this. So --

DR. KEMPER: Well, neither do I.

DR. HOMER: In terms of the criteria that we use, in other words, is there treatment available for it? Does early detection affect the disease in a way that's different than it would be if it came to apparent clinical attention? Seems that we could ask those same questions in looking at is it a severe condition?

I mean, in other words, we should be using the same kind of criteria. And so, for example, if it's not terribly severe or that early

identification doesn't really affect the course or compared to clinical treatment --

DR. KEMPER: That's exactly the tack that I took into it, and it could be that I'm just over thinking it and making my job harder related to this. Because typically, it wasn't the case that those individuals with later onset disease would be found early.

And now they're being identified through newborn screening, but it may be years and years and years before they're going to develop symptoms. We just don't have that -- those data to be able to say anything about that yet.

So what I was hoping to do then was to look at -- and there are a million case studies out there, plus or minus five. There's just a lot of case studies out there about it. And the issue is trying to tease out when exactly in these case studies that the individual who was diagnosed and trying to glean from that whether or not the early intervention made a difference.

Now it's just hard to do, and especially

because the descriptions of these later onset cases are so variable. So I've really been trying to work to get to your question. But I think at the end of the day, I just don't want to promise the Advisory Committee that I'll be able to come up with a good story around this.

The real thing that I was hoping to be able to find was at least a standard algorithm for how individuals suspected of having later onset disease would be followed up because at least then I would say this is what the impact is at least going to be on the individual, even if we don't know whether or not this early identification makes a difference.

But again, there just doesn't seem to be that consensus yet. Now I don't want to be -- over paint things too black and white because we're still in the process of doing the review. I just want to maybe ensure that everyone kind of knows what I'm struggling with.

Does that answer your question, Charlie?

DR. HOMER: It does. But it seems to me,

just based on your preliminary impression, I mean, if you created sort of a grid for the two groups, that is early and late onset, it sounds to me like your level of certainty for the later one is going to be pretty low.

So I have a feeling if you sort of frame it that way, it's not going to end up influencing our decision one way or the other. We're going to have to decide based on the early onset.

DR. COPELAND: The complicating factor for this is the treatment comes to about $200,000 a year in enzyme replacement therapy. So addition even one year early is a big health cost. So that's a lot why there's a problem with finding the protocols.

DR. BOYLE: I just wanted a clarification from Stephen's question. And that is in January, we would see the initial review, how that's digested, how it relates to the readiness and feasibility aspects, but not vote on it at that point in time?

DR. KEMPER: Well, I mean --

DR. BOYLE: I guess I would like to see those two things coming together and have a

discussion of them --

DR. KEMPER: Discussion first?

DR. BOYLE: Yes.

DR. KEMPER: Okay. Well, that makes things more comfortable for me, too, then. Right.

So I think that, you know, again, our evidence review workgroup works at the pleasure of the Advisory Committee. But given that we have a new process, I think that in terms of the work that, for example, APHL is going to be leading, I think it does make sense for us to bring it here, have a thoughtful conversation, get guidance from the Advisory Committee about what needs to be revised, and then at the subsequent meeting present the revised material and then have a vote.

I was probably too short in my answer to Dr. McDonough. But that's what I had in mind. Does that clarify things?

DR. MATERN: Yes, I had a question about the approaches to screening. And I just wanted to ensure that as you go forward, you look at how often they have to do, not just a repeat on the same blood

spot basically to confirm initial result, but actually go back and ask for a second specimen or any kind of confirmatory testing.

DR. KEMPER: That's a critical thing that we will be looking at. So that recalling a baby's - -

DR. MATERN: Right. How often do you actually have unnecessary contact with the family based on a newborn screening result?

CHAIRMAN BOCCHINI: Freddy, I'm going to give you the last comment before lunch.

DR. CHEN: Thanks.

Alex, I remember when the Pompe came up for initial, and there was a lot of concern and discussion about the late onset. I think I certainly would like to hear more information about the late onset to help with our decision-making.

It does sound like it's from the last meeting that you presented, when we talked about the nomination, in two-thirds of these cases that we identify are probably going to be late onset. We have to worry about what we're going to do with them

and who's going to follow them and how that's going to be identified and what's going to happen with them over time. Because they are all going to be in that same pool.

DR. KEMPER: I absolutely agree, and especially, too, because they present on such a wide spectrum. The best that I can say with some relative confidence -- how's that for like keeping myself from getting in trouble -- is that I think that the work that we're doing with Lisa Prosser. So at least so that we can give estimates, if you were to begin screening, well, how many of these later onset cases are we talking about?

And then the experts getting kind of a range of what the impact on those families would be. We could create the story that way, even if it's not drilled down tight. So what's a reasonable estimate in terms of the upper and lower bounds?

Would that be helpful, Freddy?

CHAIRMAN BOCCHINI: All right. Thanks again, Alex. Appreciate your presentation.

DR. KEMPER: Thank you.

CHAIRMAN BOCCHINI: We're going to conclude this morning's session, but I want to remind everybody that we're going to start promptly at 1:30 p.m. because this afternoon's subcommittee meetings have been cut short because of the schedule. So we want to make sure that we end on time to get them into their respective rooms to get started.

So I'll ask that everybody do their best to get back a few minutes early so that we can all be seated and ready to start by 1:30 p.m.

Thank you all. Have a good lunch.