THE ADVISORY COMMITTEE ON HERITABLE DISORDERS

IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS

5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Friday, August 9, 2024

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P R O C E E D I N G S

Welcome, Roll Call, Opening Remarks,

and Committee Business

DR. CALONGE: Good morning. I want to welcome everyone back to day two of the ACHDNC Meeting. Today we're going to begin with public comments, and we're going to shift to the nomination summary for Metachromatic Leukodystrophy, provided by the Nomination and Prioritization Workgroup.

Lastly, we'll have an update from the Naming and Counting Condition Ad Hoc Topic Group, and at this point I'll turn it over to Leticia for the roll call.

COMMANDER MANNING: Thank you. Good morning everyone. It's lovely to see all of you that made it here safely this morning. Lots of rain. I'm going to start with the Committee Members. From the Agency for Healthcare Research and Quality, Robyn Sagatov.

DR. SAGATOV: Here.

COMMANDER MANNING: Michele Caggana?

DR. CAGGANA: Here.

COMMANDER MANNING: Ned Calonge?

DR. CALONGE: Here.

COMMANDER MANNING: Carla Cuthbert from the Centers for Disease Control and Prevention?

DR. CUTHBERT: Here.

COMMANDER MANNING: Jannine Cody?

DR. CODY: Here.

COMMANDER MANNING: Christine Dorley?

DR. DORLEY: Here.

COMMANDER MANNING: From the Food and Drug Administration, Paula Caposino?

DR. CAPOSINO: Here. Hello.

COMMANDER MANNING: From the Health Resources and Services Administration, Jeff Brosco?

DR. BROSCO: Present.

COMMANDER MANNING: Jennifer Kwon?

DR. KWON: Here.

COMMANDER MANNING: Ash Lal?

DR. LAL: Here.

COMMANDER MANNING: From the National Institute of Health, Melissa Parisi?

DR. PARISI: Here.

COMMANDER MANNING: And Chanika Phornphutkul?

DR. PHORNPHUTKUL: Here.

COMMANDER MANNING: Now for the Organizational Representatives. From the American Academy of Family Physicians, Robert Ostrander?

DR. OSTRANDER: Here.

COMMANDER MANNING: The American Academy of Pediatrics, Debra Freedenberg?

DR. FREEDENBERG: Here.

COMMANDER MANNING: From the American College of Medical Genetics, Mira Irons?

DR. IRONS: Here.

COMMANDER MANNING: From the American College of Obstetricians and Gynecologists, Mara Black? From

the Association of Maternal and Child Health, Sabra Anckner?

DR. ANCKNER: Here.

COMMANDER MANNING: From the Association of Public Health Laboratories Susan Tanksley?

DR. TANKSLEY: Here.

COMMANDER MANNING: From the Association of State and Territorial Health Officials, Scott Shone?

DR. SHONE: Here.

COMMANDER MANNING: From the Association of Women's Health Obstetric and Neonatal Nurses, Katie Swinyer?

MS. SWINYER: Present.

COMMANDER MANNING: From the Child Neurology Society, Margie Ream?

DR. REAM: Here.

COMMANDER MANNING: From the Department of Defense, Jacob Hogue?

MR. HOGUE: Here.

COMMANDER MANNING: From the Genetic Alliance Natasha Bonhomme?

MS. BONHOMME: Here.

COMMANDER MANNING: From the March of Dimes, K.J. Hertz? From the National Society of Genetic Counselors, Amy Gaviglio?

MS. GAVIGLIO: Here.

COMMANDER MANNING: And from the Society for Inherited Metabolic Disorders, Sue Berry?

DR. BERRY: Here.

COMMANDER MANNING: Okay. And that's roll call, and while I have the mic, I'm just going to go over a few things. We went through them yesterday, but just some reminders. This is a FACA meeting, and all Committee Meetings are open for the public. If the public wish to participate in the discussion, the procedures of doing so are published in the Federal Register, and as Ned stated previously, we will be having public comments today.

Only with advance approval from the Chair, or the Designated Federal Official, which is myself, may public participants question Committee Members or other presenters. In regards to --- oh, in regards to the building. Visitors only have access to the fifth floor, that's the floor that we're on. It's not one, it's five-.

We are in the pavilion area. The cafeteria is across the way there. There's a store back that way, and there are bathrooms here, here, here, and here, behind us, so lots of bathrooms. Visitors are not allowed to take videos or photographs in the building, and please do remain on the fifth floor. Next slide please.

If you need to leave the building you will need an escort to reenter, so we are encouraging folks to stay in the building for the duration of the meeting, but if you do need to leave, please notify HRSA staff. There's a team of folks back in the corner there, if you

could just raise your hand if you need anything, they can help you, thank you. -Next slide please.

If for whatever reason we have to evacuate the building, you will evacuate the way you came in, and there's a parking lot to the left of the building. You'll see people moving out that way, and we'll just walk out there together. Next slide please.

For ethics, I must remind all Committee Members that you must recuse yourself from participation in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner, unless you are also an employee of the organization, or unless you have received a waiver from HHS authorizing you to participate.

So, as in the case today when a vote is scheduled, and there is a vote scheduled, or an activity is proposed, and you have a question about a potential conflict of interest, please notify me immediately. You

can also speak to the Chair. And I am going to turn it back over to Ned, thank you.

DR. CALONGE: Thanks, Leticia, and I want to thank the Committee Members, and the Organizational Reps for reviewing the May 2024 meeting summary. I'll ask one more time are there any corrections to the meeting summary before we vote to approve? Seeing none, can I have a motion to approve the meeting summary?

DR. KWON: I move to approve.

DR. CALONGE: Thanks, Jennifer. Is there a second?

DR. CODY: I'll second.

DR. CALONGE: Thanks Jannine. Leticia, would you do the roll call vote?

COMMANDER MANNING: Sure. Now, this is the real test to get everyone's name correct the second time. Okay, from the Agency for Healthcare Research and Quality, Robyn Sagatov? It's too much pressure.

DR. SAGATOV: Yes.

COMMANDER MANNING: Michelle Caggana?

DR. CAGGANA: Yes.

COMMANDER MANNING: Ned Calonge?

DR. CALONGE: Yes.

COMMANDER MANNING: Carla Cuthbert?

DR. CUTHBERT: Yes.

COMMANDER MANNING: Jannine Cody?

DR. CODY: Yes.

COMMANDER MANNING: Christine Dorley?

DR. DORLEY: Yes.

COMMANDER MANNING: Paula Caposino?

DR. CAPOSINO: Yes.

COMMANDER MANNING: Jeff Brosco?

DR. BROSCO: Yes.

COMMANDER MANNING: Jennifer Kwon?

DR. KWON: Yes.

COMMANDER MANNING: Ash Lal?

DR. LAL: Yes.

COMMANDER MANNING: Melissa Parisi?

DR. PARISI: Yes.

COMMANDER MANNING: And Chanika Phornphutkul?

DR. PHORNPHUTKUL: Yes.

COMMANDER MANNING: Thank you.

DR. CALONGE: Motion passes. Thanks everyone.

Public Comments

DR. CALONGE: We're going to now move into the public comment period. We received a letter of request by individuals to provide oral, public comments to the Committee today. Some individuals are here in person, and other will join us virtually, and I think we have an extra person who is signed up with their parents, so that's wonderful.

We also received seven written public comments that were shared with the Committee Members, and I'm sure we have all reviewed those, and thinking about the information that was included within them, so

I'd like to move to the oral public comment. Our first person is Lauren Stanford.

MS. STANFORD: Good morning. Hi. Members of the ACHDNC -- my name is Lauren Stanford, and I'm the Senior Director of Advocacy at Parent Project Muscular Dystrophy. On behalf of the estimated 15,000 individuals living with Duchenne in the United States who underwent the extensive, expensive, heartbreaking and avoidable diagnostic odysseys, I am here to continue to advocate for the addition of Duchenne to the recommended uniform screening panel, also known as the RUSP.

The addition of Duchenne to the RUSP will not only ensure ----

COMMANDER MANNING: Lauren, I'm sorry, there's something wrong with the mic. We want to hear you.

MS. STANFORD: Are you sure? I'm sorry. Am I good to keep going where I started, or should I start

over?

COMMANDER MANNING: You could start over.

MS. STANFORD: Great, okay. Hi, my name is Lauren Stanford, and I am the Senior Director of Advocacy at Parent Project Muscular Dystrophy. On behalf of the estimated 15,000 individuals living with Duchenne in the United States who underwent the extensive, expensive, heartbreaking and avoidable diagnostic odysseys, I am here to continue to advocate for the addition of Duchenne to the RUSP.

The addition of Duchenne to the RUSP will not only ensure that future babies born in the U.S. will avoid the irreversible consequences of the diagnostic odyssey, but will also enable opportunities to introduce timely interventions during optimal, therapeutic windows.

Duchenne is a progressive, genetic, multisystematic disorder. It robs children of their ability to walk and raise their arms. It can also

significantly impact developmental endocrine, bone, heart and lung function, and is almost always- fatal before age 40, and tragically sometimes even decades sooner.

PPMD has been tirelessly working towards the inclusion of Duchenne in newborn screening for over a decade. Our efforts aim to ensure timely diagnosis and optimal timeframes for interventions, and to enable the best possible outcomes for every baby born with Duchenne.

Today, we are at a pivotal moment with our ability to enhance health outcomes for those with Duchenne. With a clear understanding of how crucial it is to address developmental delays early, coupled with eight recent FDA-approved therapies that alter disease progression, and a promising pipeline of new treatments, the importance of early and equitable diagnosis cannot be overstated.

The timely diagnosis not only provides access

to lifechanging therapies, but also alleviates the strain of delayed detection for families. Early identification is about more than just extending life. It's about significantly improving its quality, and empowering families to face challenges ahead with greater preparation.

Without newborn screening, patients and their families are often deprived of the opportunity to make fully informed medical decisions when there is still muscle to be preserved. We greatly value our partnership with the ACHDNC, and thank you for approving our community's request to postpone the vote on this matter as new evidence is prepared for your review.

PPMD is currently driving multiple projects that will have a direct impact on our body of evidence. My colleague, Megan Freed, will speak to the projects that are underway in her comments. The addition of Duchenne to the RUSP will recognize the urgency of timely intervention in Duchenne, and the profoundly

positive impact we can have with children with Duchenne when we introduce clinical and therapeutic resources immediately.

Thank you to the Committee for your continued attention to the Duchenne evidence review. As a Committee – as a community, sorry -- we have laid the groundwork, we continue to strengthen the evidence for review, and we are creating innovative solutions for long-term- data collection and care standards.

Together, we can change the trajectory of this devastating disease, offering hope and a brighter future to those affected by Duchenne Muscular Dystrophy. Thank you.

DR. CALONGE: Thank you. Next, we have Megan Freed.

MS. FREED: Good morning. Thank you to the Committee for the opportunity to testify today. My name is Megan Freed, and I'm the Director of Data and Technology Strategy at Parent Project Muscular

Dystrophy. I'm excited to update the Committee on a groundbreaking project being led by PPMD. This project addresses a crucial need to quantify the benefit of early intervention with steroid treatment on young children with Duchenne.

Our goal is to provide the ACHDNC with comprehensive, and empirical evidence that earlier treatment of Duchenne delays the progression of disease. The primary objective of our project is straightforward, yet transformative. We seek to gather and analyze data to determine whether a timely diagnosis of DMD defined as before age four years, followed by the initiation of corticosteroid treatment, yields better health outcomes compared to starting treatment at the current median age of diagnosis, defined as five years of age.

This investigation will be instrumental in informing future recommendations and treatment protocols. Our study is built on three core aims. Number one, to evaluate the impact of early

corticosteroid treatment. We will assess if initiating corticosteroid treatment very early in the diagnosis and disease trajectory is linked to delayed loss of ambulation.

This means determining whether starting treatment sooner helps patients maintain their ability to walk for a longer period of time. Number two, to analyze disease trajectory. We will examine whether early initiation of corticosteroids correlates to an improved disease trajectory as measured by standard neuromuscular functional tests in the clinical setting.

This will help us understand if early treatment translates to better overall functional outcomes. And number three, to assess pulmonary function maintenance. We will explore whether early treatment contributes to longer maintenance and pulmonary function, which is critical for the quality of life of DMD patients.

In other words, does earlier steroid

treatment allow DMD patients more autonomy of getting up off the floor, climbing stairs and playing with their friends, does it allow more patients more months or even years of walking? Can they breathe longer on their own without the respiratory support of machines?

To achieve these aims we're working with four exemplary academic medical centers to closely review and analyze their patient's course of treatment in clinical outcomes. Our project hinges on data completeness, data sharing, and expert analysis to prove statistical significance.

It's our hope that this analysis will be ready for the Committee's review in mid-December. By systematically assessing the relationship between early intervention and clinical outcomes of Duchenne, this project will not only advance our scientific understanding, but potentially improve the standards of care for patients.

We look forward to continuing to update the

Committee on the progress made in this project, and thank you very much for your continued commitment to our nation's newborns.

DR. CALONGE: Thank you. Next, online we have Samuel MacKenzie.

DR. MACKENZIE: Hi there. Good morning. On behalf of the Duchenne Clinician Community, thank you for the opportunity to testify today. My name is Dr. Sam MacKenzie. I'm a child neurologist with additional certification in neuromuscular medicine, practicing at the University of Rochester.

The University of Rochester is a certified Duchenne care center, and currently supports approximately 150 patients with Duchenne and Becker Muscular Dystrophies. I am fortunate to practice in New York State, where we successfully piloted DMD newborn screening from 2019 to 2021, and legislation to begin screening broadly goes into effect later this year.

This is a crucial step forward. Despite over

30 years of efforts to improve clinical identification of Duchenne through CK screening, diagnosis delays persist. The average age of diagnosis remains at 4.9 years, a delay that continues to be a significant challenge and is increasingly damaging, given the expanding array of treatment options available.

The benefits of newborn screening for Duchenne are substantial. Early screening allows for the prompt implementation of standard of care, including early intervention services and consideration of corticosteroid therapy as we've just heard. It also provides earlier access to newly approved disease modifying medications, such as exon skipping therapies and gene therapies, at a stage when muscle damage and fibrosis are minimal.

Additionally, it enables participation in clinical trials without the risk of aging out, and it gives families valuable time to understand the disease and explore treatment and trial options. Today, we have

a growing arsenal of treatment options with eight FDA-approved therapies and more on the horizon.

Early diagnosis and intervention are crucial, as delays can lead to irreversible muscle damage that could have been mitigated with timely use of corticosteroids and other disease modifying treatments. Newborn screening allows for early diagnosis before children start school, facilitating the early evaluation and identification of learning disabilities.

It also provides families with timely genetic counseling, helps identify carriers who may face their own health concerns, and supports the development of social support networks. Importantly, it allows families to make informed decisions about integrating the diagnosis into their lives, which can influence many aspects of their future, including housing and other critical choices.

So, for these reasons I strongly support the implementation of Duchenne newborn screening by adding

it to the RUSP, and I appreciate your attention and dedication to advancing this crucial initiative. Thank you.

DR. CALONGE: Thank you. Next we have Paul Melmeyer, who I thought was --- oh, he's virtual today, okay. -Sorry, Paul.

MR. MELMEYER: Here I am. Apologies all. All right, I'll get going. Thank you for the opportunity to comment on the ongoing review of Duchenne Muscular Dystrophy for consideration for the recommended uniform screening panel. I am Paul Melmeyer, Executive Vice President of Public Policy and Advocacy at the Muscular Dystrophy Association.

MDA is proud to serve the Duchenne Muscular Atrophy and Pompe community, along with many other rare neuromuscular disease communities. I want to again thank the Committee for agreeing to extend the review period of our Duchenne Muscular Dystrophy nomination, and are grateful for the work of Dr. Kemper, the

evidence review group, and the technical expert panel.

This delay will allow us to continue collecting evidence on the importance of earlier administration of treatments for the Committee to consider as already detailed by our co-nominators at Parent Project Muscular Dystrophy. Since last we met the FDA has expanded the label of Elevidys, the first and only FDA--approved gene therapy for DMD.

From an accelerated approval for those four and five years of age to a full approval for all ambulatory individuals over the age of four, and an accelerated approval for all non-ambulatory individuals. The label expansion will allow many more in the Duchenne community to consider Elevidys as an option.

Finally, we would like to comment on the Duchenne nomination discussion from the previous ACHDNC Meeting. To start with, we urge the Committee to not re-adjudicate FDA's decision making. The FDA is the sole regulatory agency determining whether a therapy is

safe and effective, and we see no reason for why this Committee should re-analyze to reconsider a therapy's effectiveness, when the FDA has already done so.

Second, we reiterate once again that there is no presymptomatic phase of Duchenne, as was stated several times in the previous meeting. As indicated by elevated CK at birth, muscle damage is occurring from the moment a baby is born, and just because we don't clinically observe those symptoms occurring for a few years, does not mean that they are not happening.

We encourage the illumination of this phrase. There were also several points made last meeting that we would like to support and reiterate. First, we greatly appreciate the ERG closely investigating nonpharmaceutical benefits at an earlier diagnosis, including avoiding -the diagnostic odyssey, effects on the family, family planning and improved health status prior to gene therapy eligibility and more.

We are similarly grateful for the

acknowledgement of parental perspectives, including discussion of the study indicating a clear preference for an earlier diagnosis. We agree with the comments debunking gene therapy as unrepeatable due to antibody acquisition from the AAV as we and many others in the field are making rapid progress at redosing and non-AAV approaches.

Finally, we would like to emphasize the "stream of evidence" suggesting that there may be benefit from earlier "corticosteroid initiation," presented by Dr. Kemper, and again seek to only reiterate this conclusion in our ongoing work with PPMD.

Again, very grateful for the Committee's continued review, and thank you for the opportunity to testify.

DR. CALONGE: Thank you. I'm going to move on then to Sanjiv Harpavat. I guess he's not on, so next Peter Kyriacopoulos.

DR. HARPAVAT: Oh. I am here, sorry, Dr.

Calonge. Can you guys hear me?

DR. CALONGE: I apologize, sorry.

DR. HARPAVAT: No problem. There was a little delay in getting on. Thank you, we're very, very grateful to the Committee in general for hearing us, and also for the expert panel for giving us the invite recently on what we're about to talk about. We're not asking for anything in this, it's more a message of thanks, and a little information.

So, I'm a liver physician. I care for patients with a serious disease called biliary atresia. This is a disease that affects 1 in 10,000 infants, and for those of you who haven't heard of it, it is rare, but in fact it's the leading indication for pediatric liver transplantation in children, as well as all organ transplantation in children, and all the morbidity and mortality that comes with it.

So the hope for me, with this disease, is that we know that large retrospective studies with

hundreds of patients, over many countries, over dozens of years, have shown that earlier detection of this disease helps prevent the transplant burden, reduce the transplant burden.

We are really encouraged that science tells us that earlier detection and treatment helps alleviate liver transplants. The problem is that although the disease is present at birth, babies look healthy initially and are often detected at later times, and this later treatment is really what leads to the need for a liver transplant.

So, our big challenge, and when I say our I include all the people in the room, all the people with expertise in helping children born in the United States, is to develop an acceptable test that we can use to detect babies with biliary atresia earlier.

We're completely committed to newborn treating for biliary atresia, exploring all possibilities, and we very much appreciate the

Committee's advice, suggestions and guidance, in trying to figure out what's the right test right now, the point of care test, and we understand and appreciate now the challenges with the point of care testing, and that was given by the testimony yesterday, the talks yesterday.

We're constantly learning from you. We appreciate the value of thinking carefully about implementation with that in the context of the enormous, but very, very, important work that is taking place every day in the state newborn screening laboratories. There's more to come, but this is just an introduction to the disease. Again, thank you very much to the Committee, for starting to think about biliary atresia.

DR. CALONGE: Thank you, Dr. Harpavat. Next, we have Peter Kyriacopoulos.

MR. KYRIACOPOULAS: Thank you very much. So, I'm Peter Kyriacopoulos. I am the Chief Policy Officer for the Association of Public Health Laboratories, APHL, where I have been working on newborn

screening issues with my colleague, Jelili Ojodu, for over the past two decades.

I want to thank the Committee for its attention. I want to thank our HRSA friends for facilitating the placement of some slides that I developed for the Committee's consideration as well. So, I think you all know, APHL works to improve the operations of state, local and territorial public health laboratories, and we also work to help improve the operations of our federal partners, the Health Resources and Services Administration, Centers for Disease Control and Prevention, and the Food and Drug Administration.

So, we can see a little bit of that indication of that help if you look to the modest increases in federal funding that had been coming into the newborn screening activities at these federal partners. The FDA has issued a final rule on LDTs is what we're calling it, there's a bigger name, and we have been monitoring this issue for the past dozen

years.

We have been providing comments, and if you go to the slide deck you'll be able to get links to all of the comments that we have submitted. We are the -- I think the perhaps only laboratory organization that is not opposing the FDA activity on LDTs. And in fact, we are trying to inform FDA about the work of public health laboratories, especially when it comes to newborn screening, so that they are aware of the steps that they can take to prevent any harmful disruptions, I think is the easiest way to say that.

So, what am I talking about? Public health laboratories have not been engaged with the findings of paperwork that the FDA asks for, and this may surprise you, but they actually are not funded to have staff who might be able to respond to the FDA. So, we are trying to learn best for our members' sake how they can comply with this new requirement.

And we've been fortunate, I think, being able

to share information with FDA that they have then incorporated into some of the initial guidance documents that they have produced, and we know that they are working on producing more informational guidance documents, and also webinars to help with compliance.

Again, in the slide deck I shared, you will find reference to the website that APHL will develop, and that will be public facing, so you all can see all the information that we have on lab developed tests and compliance with the FDA rule. We are obviously very concerned that there are very few disorders that when they are added to the RUSP, they actually have an FDA-cleared test.

And in fact, in our information is it takes three to five years after a disorder is added before there is an FDA-cleared test. Because of that length of time, we have urged FDA to consider putting newborn screening testing under the imminent health threat issue in the guidance document that they have developed

because many, many states, as soon as the disorder is added to the RUSP, they must begin to implement that disorder.

So, we think that that is an imminent addition that requires attention sooner than a three to five years that you might get an FDA-cleared test through. We know that there have been some actions by states already that are concerned about what they must do next. So, again, I want to thank the Committee for its attention, and let you know that there's much more to come from APHL. Thank you.

DR. CALONGE: Thank you, Peter. Next we have Dean Suhr.

MR. SUHR: Good morning. Thank you for your attention this morning, Chair and Committee Members. I'm Dean Suhr. I'm an MLD father and President and Co-Founder of MLD Foundation. I'm honored to be here to present the RUSP nomination for Metachromatic Leukodystrophy. It's a day that so many of us,

including many families who are watching online have been waiting for, for a long time.

I'm humbled to represent the entire MLD community, including the 84 families that we know of that have lost a loved one to MLD over the past five years. Deaths that could have been changed to not only alive, but thriving, and all but 100% normal if only they had been identified by newborn screening, instead of post-symptomatically when therapies would not work for them.

So let's build a stool. If you know a stool, two legs doesn't work. You need more than two legs. I'm going to talk about that very briefly. First leg, viable therapy. In 2005 MLD Foundation first met with the gene therapy research team from Milan, along with several dozen MLD experts all of whom said gene therapy would not work. They were wrong.

We worked with them through animal studies, clinical trials, EMA approval, and 19 years after that

first meeting earlier this year in March we got an FDA approval for gene therapy. The MLD community has more longevity outcome data on that gene therapy than any other gene therapy that I'm aware of.

I can tell you because I've personally seen it, the therapy has all but perfect outcomes when accessed pre-symptomatically. The data in front of you in our packet, and the testimony from families you have, and will hear from demonstrate this.

The first human patient is now 14 years post-transplant, post gene therapy. These are gene therapy patients now in their teens, they're attending school, they're running, jumping, playing and excelling in their classwork. Second leg, an accurate, repeatable and replicable newborn screening assay. Professor Geld, with some prodding and questioning by my wife, Teryn, came up with a technique to avoid the 8% pseudo deficiency false positive rate that MLD has.

They validated and piloted the first testing

for elevated sulfatides substrate levels using standard newborn screening dried blood spots, standard cards, on tandem mass, and relegated the ARSA enzyme level testing to the second tier. The third tier of genomic sequencing, to help predict the form of the disorder.

The de-identified results were astonishing. Subsequently, the assay has been piloted in a half dozen labs, including Screen Plus in New York, and numerous sites over in Europe. With over a quarter million spots screened, four babies have been identified, and are referred to, or awaiting therapy with zero false positives.

Those of you that know Michael Gelb know that he would have shared those last two statements much more emphatically than I just did, and I know he's watching right now. The data that you have clearly demonstrates that the assay fits all of the RUSP criteria, and yes, we have achieved the N-of-1 criteria.

Legs three and four are not really RUSP

criteria, but they're important, nonetheless, and they're something that I've heard you discuss. Value. It's important to be aware of it. ICER here in the U.S. and NICE, the U.K. State organization chartered with value assessments, both used the same rigor to assess value that Dr. Kemper's external evidence review group uses to look at the science of the proposed screens, and the efficacy of new therapies.

ICER and NICE both reviewed Lenmeldy for the therapeutic efficacy and its value to patients and the taxpaying societies they represent. Lenmeldy proved to a great value on both continents, meaning that the one-time upfront cost of therapy paid for itself after just a few short years because this therapy is essentially curative, there's no ongoing medical cost.

A fourth leg, and this was discussed a little bit yesterday, access or reimbursement. Yesterday we briefly discussed Medicaid across state lines. How does one state credential refer and then pay for therapy in

another state? There will be five centers of excellence for the MLD therapy in the U.S.

Most patients will be crossing state lines to access the therapies, and looking across the panel, and I don't see Dr. Kemper here, but all of you will be sending patients to another state because you're not one of those five states.

I'm from Oregon, this is my third trip to D.C. over the past 60 days. Typical with each two-day trip is 16 to 25 Hill office visits to promote Medicaid and para legislation. I'm working with a team of advocates to write some of this legislation, and we hope for three access and reimbursement bills to advance to floor votes this session, and I would appreciate the opportunity to show more about that maybe at a future meeting, kind of the bigger picture in that umbrella.

So, that's four solid legs that we have for MLD therapy and newborn screening. In closing, I want to thank the many dozens who have worked, some for over

a decade, on MLD newborn screening in the nomination. You can see many of their names in the nomination package. The data clearly and strongly supports our request for acceptance and referral to external expert evidence review.

As has been the case for almost 15 years, the MLD community is at your service to answer questions, refer you to additional data experts and other resources. Some of those experts are in the audience today. If there are any questions that come up during your discussion that we can quickly answer, we'd be happy to do that.

So, unlike many of you who probably have pictures of your family on your phone, my home screen is a picture of a very young boy, who is burying his younger brother. His younger brother died from MLD. He doesn't know what he's doing, and that's probably a good thing, but I hope that when we get newborn screening onto the RUSP, and we get it implemented in 50 plus

states and territories, that I could pick the pictures of my grandkids back onto my phone, so please help me do that, if nothing else, approve it so I can do that.

As always, we appreciate and thank you for the hard work of the Committee, and the public health system on behalf of the children, and frankly as they grow up healthy adults of America, thank you.

DR. CALONGE: thank you. Next, Maria Kefalas.

MS. KEFALAS: I am ceding my time to my dear friend Amy Price and her son Giovanni Price. I will simply say that Amy and I have waited a very long time for this moment. I'm very pleased to introduce to you this amazing advocate and mom who will share her story of gene therapy on behalf of the families who have lost children, and the families who will not suffer as we have, thank you. Come on up.

DR. CALONGE: This is Amy and Giovanni Price.

MS. PRICE: Hello, thank you. My name is Amy

Price, and this is my son, Giovanni. We are here today to ask that Metachromatic Leukodystrophy be advanced towards approval for the RUSP. Giovanni will begin his last year of middle school in two weeks, an eighth grader who loves football, watching weather chasing videos, and his cats. Giovanni is an amazing cook. He has mastered omelets that I have never been able to master, and he makes the perfect grilled cheese.

He knows everything about cars and has talked about going to a college in Kansas that specializes in historic car restoration. Everything about Giovanni mirrors that of the average, ordinary 14-year-old boy. His friends, peers in school, or anyone who meets him would never guess that in 2011, at 11-months-old, he was diagnosed with late infantile Metachromatic Leukodystrophy, and that just three weeks after that he was on a plane to Italy, where he became the second child in the world to undergo gene therapy for MLD.

I cannot talk about Giovanni without talking

about his sister Liviana, who is almost exactly two years older than him. Due to a lack of newborn screening for MLD, and a pattern repeated in many families in the U.S., Giovanni's sister's symptomatic diagnosis led to his diagnosis.

Liviana adored Giovanni. I can never talk about her without crying. She called him Gimanni, and she said that he was her best friend, before she lost the ability to speak. She followed him around and always wanted to hold his hand to keep him safe, before she lost her ability to walk. While Giovanni was receiving his lifesaving gene therapy, Liviana was losing every single milestone she ever attained, becoming dependent on tube feedings, and crying in pain for her body's betrayal.

It is difficult to describe the pain of saving one child while losing another to the same condition. We lost Livi in 2013 at just five and a half years old. She left behind not just her dad and I, and

Giovanni, but other siblings who feel the heavy weight of her absence in their lives.

The impact of sibling loss and sustaining grief never goes away. We frequently talk about Liviana and see her photos, memories and stuffed animals on a shelf in the center of our home. She would be 16 years old if still alive today. I never thought it would have taken 13 years after Giovanni's treatment to have gene therapy finally approved in the U.S.

And given all we know about the absolute critical importance of early diagnosis of MLD to save lives with gene therapy, I never thought we would be here today with an approved therapy, but without an approved newborn screening. Until we have both we will continue to lose children to this cruel and devastating disease.

Parents will continue to tell the story of pain and loss and siblings will grow up with longing grief. As a parent who has lived the reality of gene

therapy saving one child's life, and a diagnostic delay taking another, I cannot implore you enough to move swiftly in approving MLD to the recommended universal screening panel.

And Giovanni is going to say a few words now.

MR. PRICE: My name is Giovanni Price. You've heard a lot about me. I was only one when I had my gene therapy, so I do not remember it. I look at photos and talk to my parents about the experience. Only my closest friends know about my MLD and gene therapy. They don't really understand and how I have terminal --- how- is it terminal?

But I'm here living a normal life instead, and it's hard for me to understand sometimes. I do all the same things my friends do. I get good grades. My teachers have told me I'm a really good writer, I like to make presentations for my class and playing football games. I was only three when Livi died. I feel like I remember her so well.

I remember playing with the little rocks on her bed. We have so many photos of her, and my parents telling me stories. Playing with her, or trying to help take care of her. When I would hear her coughing, and my mom talks about her saying I was her best friend, it makes me happy and sad at the same time.

It is sad to have lost not only a sister, but a best friend. Sometimes it is really hard to understand why I am here, but she is not. I see how sad my family is about Livi not being here. We celebrate her birthday in January and her time in heaven in September, and we look at her photos and talk about the funny things she would do.

I know that without gene therapy my parents would only have photos on the shelf, and have to talk about memories of me with tears in their eyes. I also know that without newborn screening more parents will be left just memorized in photos. Please for all the sacrifice and tears we ask you to approve MLD to the

newborn screening panel.

DR. CALONGE: Thank you. Next online we have Barbara Burton.

DR. BURTON: Good morning, and thank you so much for giving me the opportunity to testify in support of sending the nomination of Metachromatic Leukodystrophy forward for a full evidence review. My name is Barbara Burton. I'm a Professor of Pediatrics at the Northwestern University Feinberg School of Medicine, and Co-director of the Leukodystrophy Care Center at the Lurie Children's Hospital of Chicago.

In the latter capacity I care for children and families affected by MLD and have done so for over 40 years. Early onset MLD is a genetic disorder that devastates both the child and the entire family. Symptoms typically begin between two and eight years of age when a child who previously seemed to be completely healthy and normal develops motor symptoms such as a clumsy or staggering gait, or frequent falls.

Once the symptoms appear, the disease progresses rapidly to cause degeneration of both the brain and the peripheral nerves. As a result, affected children rapidly lose the ability to walk, talk, eat and move. After the onset of symptoms there is nothing medically that can be done to stop the relentless progression of the disorder, which is ultimately fatal, often after years in a severely, neurologically impaired state.

The only treatment that can be provided is symptomatic. This year, as you've heard, a truly lifechanging form of gene therapy was approved by the FDA for treatment of early onset MLD. This is perhaps the most dramatically effective new therapy for a genetic disorder that I have witnessed in my long career as a medical geneticist.

You just saw an incredible example of this in Giovanni Price. If the treatment is provided before the onset of symptoms, the treatment can dramatically alter

the course of the disorder, allowing the affected child to live a normal life, going to school, and interacting with family and friends like any other healthy child.

Sadly, however, it is not effective after symptoms have emerged, and the diagnosis is established on clinical grounds. Currently, it is only possible to make the diagnosis in a child prior to the onset of symptoms if they have an older, affected sibling. This is why newborn screening is absolutely critical for this condition.

A family should not have to lose one child to the disease before another can be saved. Newborn screening has been shown to be effective in accurately identifying the condition and pilot programs and is likely cost effective when considering the extraordinary financial and emotional costs of caring for severely neurologically impaired child with MLD for up to 20 years.

It's time to save the lives of those children

born each year in our country with this devastating disease. You can make that happen by voting to send forward the nomination of MLD for addition to the RUSP. Thank you for all that you do to advance newborn screening for our children.

DR. CALONGE: Thank you. I'd like to return to the topic of DMD and welcome Lindsey Flessner who is online.

MR. FLESSNER: Hi. I'm actually Daniel Flessner, I'm Lindsey's husband.

DR. CALONGE: Sorry, Daniel, thanks.

MR. FLESSNER: What's that?

DR. CALONGE: I apologize.

MR. FLESSNER: No, we're fine. I want to start off with thanking you all for giving me this opportunity to share a story today, and for listening to how Duchenne Muscular Dystrophy has profoundly impacted our lives, and why I believe it's critical that this should be added to the RUSP.

On June 16, 2021, our world has forever changed. Our oldest son, Mason, at just three years old was diagnosed with Duchenne Muscular Dystrophy. The news hit us like a freight train. As if that wasn't overwhelming enough, we were advised to have our youngest son, Dawson, who was only six months old at the time be tested as well.

To top that off, we were told my wife, Lindsey would need to be tested to determine if she was a carrier. Diagnosis felt like an unstoppable force, flattening our lives in an instant. We were thrust into a whirlwind of establishing a care team, reorganizing our schedules, and trying to maintain some semblance of normalcy for our family. Everything changed overnight.

But rather than recounting the heartache and despair we felt initially, I really want to focus on the glimmer of hope that has emerged. The landscape in Duchenne Muscular Dystrophy has evolved since that fateful day. We now see a future filled with promise,

with new therapies and gene treatments on the horizon.

When Mason was diagnosed it felt like we were racing against the clock, but now with advancements in gene therapy in newborn screening, the hope is stronger than ever. Newborn screening offers family a crucial advantage that provides an early diagnosis, allowing us to take proactive steps, rather than reacting to an urgent crisis.

With early detection families can assemble the best possible care team and explore various treatment options well before the disease progresses. This early intervention can make a significant difference in managing Duchenne and improving the quality of life. As a father deeply invested in this fight, every moment is precious. I've spent countless nights awake grappling with the reality of how to buy us more time.

Time is muscle, a concept that resonates deeply with us. By adding Duchenne to the RUSP we can

give families the gift of time, time to make informed decisions, time to seek out the best treatments, and time to fight for a better future. I'm just a farmer from central Illinois, but I've witnessed the impact of muscular dystrophy on families in ways many haven't.

Taking over the family farm from my dad I thought one of the hardest challenges would be managing our crops. But now our greatest challenge is raising hope, awareness, and striving toward a cure. To end, I want to thank each and every one of you for your time today, time that we can't get back, but together we can make a difference.

Let's stay united and say not today DMD, thank you all.

DR. CALONGE: Thank you, Daniel. This concludes our public comments for today. I want to pause and thank everyone that gave public comment, but especially parents and the children of parents who demonstrate the importance of newborn screening, follow-

up and treatment, and kind of help us realize why we're- all here, why we commit the time and effort, and emotion to this work.

Thanks for coming. Thanks for sharing your stories. These are important things for us to bring into the decision making, and help move newborn screening forward, so again, I thank you. I would like at this time to just put in a five minute break, let us do a little stretch break, and then we'll come back and have a presentation from the nomination and prioritization Committee, thank you.

Metachromatic Leukodystrophy (MLD) Nomination Process

DR. CALONGE: Welcome back, just to kind of summarize the progress so far. The Committee received a nomination to include Metachromatic Leukodystrophy to the recommended uniform screening panel through our new nomination process.

They completed step one, the four questions,

which was reviewed by the Nomination and Prioritization Committee, who felt that the questions were answered appropriately, and then the advocates supported a full nomination package, which has also been approved -- I'm- sorry, reviewed by the N and P workgroup.

So today, two members from the Nomination and Prioritization Workgroup are going to provide the Committee with a summary and recommendation as to whether or not MLD should forward to a full evidence review. Before we continue with the session, if there are committee members that feel they should recuse themselves, you may do so at this time.

And I believe that Christine Dorley has recused herself. So, Doctors Caggana and Phornphutkul are going to provide the nomination summary for MLD. Dr. Michele Caggana is the Deputy Director for the Division of Genetics, and Chief of the Laboratory of Human Genetics, and Director of the Newborn Screening Program for the New York State Department of Health.

She's also the co-lead of the genetic testing section for the clinical laboratory evaluation program. Michele works closely with NICD, CDC, and HRSA as principle investigator on several ongoing grants and contracts. She's- actively involved in several associations, the Public Health Laboratory Committees, and subcommittees.

Dr. Chanika Phornphutkul is the Director of the Division of Human Genetics, Department of Pediatrics, at the Warren Alpert Medical School of Brown University in Providence, Rhode Island. She has practiced genetics and metabolism for the past 16 years.

At the clinical level, Dr. Phornphutkul has been involved with identifying rare disorders, clinical trials and supporting families with genetic conditions. At the educational level she is the course director of the medical school's genetics curriculum, and a long-term member of the Newborn Screening Advisory Committee to Rhode Island Department of Health.

So Michele, I think you're going first. No, Chanika is going to go first.

DR. PHORNPHUTKUL: Thank you. So, on behalf of the Nomination and Prioritization Workgroup, we're happy to share information that we have worked on in the past few months. So, the nomination for Metachromatic Leukodystrophy, MLD, include the name on this list, MLD Foundation. Next slide.

Next slide please. Thank you. Sorry about that. This is the list of the people who have worked on nominating the MLD for the nomination from the MLD Foundation. Next slide. The nominated condition is for early onset both types, Metachromatic Leukodystrophy, and moving forward will be called MLD.

Next slide. Brief clinical information, MLD is an autosomal recessive condition, which results in life shortening. It is caused by dysfunctional Arylsulfatase A enzyme, ARSA, leading to a build-up of sulfatides. The sulfatide build-up affects central

nerves, central nervous system, peripheral nervous system, and as well as invoked inflammatory response. Next slide.

The clinical presentation, the prevalence is estimated to be about 1 in 40,000 to 1 in 100,000. As mentioned earlier, there are two major subtypes, early onset, and late onset. The early onset is the one that's being nominated for newborn screening. Early onset is divided into two subtypes, Late Infantile onset. Children typically present with motor delays, followed by pretty predicable decline and death in early childhood.

The other subtype of early onset, it's called Early Juvenile, which the onset is slightly later. Children often present with behavioral, cognitive changes, followed by progressive loss of motor function, and death in adolescence.

The other subtype is called onset neuropsychiatric symptoms, which are variable

presentations. However, the management for early onset, both late --- sorry, next slide. Management includes- early onset recommendation for late infantile and early juvenile.

Typically, the onset of the condition is between 30 months to seven years of age, and the recommendation of treatment is Lenmeldy, which is a gene therapy, which is the target of the screening. For late onset of late juvenile to adult form, the onset is usually seven years to older. Currently, the recommendation is monitoring and treated with hematopoietic stem cell transplantation at some point. Next slide.

The core requirements for nomination that need to be considered include the validity of the laboratory test. Number two, widely available confirmatory testing with a sensitive and specific diagnostic test. Number three, a prospective population-based pilot study. Next slide.

The key questions that we, as a subgroup needed to address, include the following nine topics. I will discuss the first two, and then we'll hand over -- sorry, next slide. So the key questions that we need to address include these nine topics. I will address the first two, and will hand over the presentation to Dr. Caggana. -Next slide.

Key question one, is the nominated condition medically serious? We concluded that the answer is yes based on the clinical presentation that I discussed earlier. Early onset both late infantile and early juvenile children have significant shortening life expectancy. Late onset has variable symptoms. Next slide.

Key question 2, is the case definition and the spectrum of this condition well-described to help predict the phenotypic range of those children who will be identified based on population based screening. Our answer is yes. The onset age onset of early onset

subtype for late infantile it's under 30 months, and for early juvenile it's between 30 months to seven years.

That accounts to up to 60% of children with MLD. There is some genotype phenotype correlation, but not definite. Null variants are thought to be more severe, and there are some common variants that align with phenotype. Newborn screening, however, will detect late onset patients. The target for the presymptomatic treatment is of the early onset. Next slide.

DR. CAGGANA: All right. Thank you. I will cover the remaining key questions. So, key question three is are prospective pilot data from U.S. and/or international from population-based assessments available for this condition? And the answer is yes. You've heard a little bit about the multinational and multiinternational studies.

One of the largest ones was from Hanover, Germany, where they screened almost 110,000 babies. They used a mix of three different sulfatides during

this pilot study for the first tier test. Of the 109,000, 381 screened positive for the first tier, so that was about 1 in 287 babies screened.

They did change parameters over time, meaning that they altered the cut-off over time, and so it was a little difficult to assess when that occurred. Then that would impact the number of screen positive babies that the sulfatide first tier test. Of all of the samples that they had of the 381, only 230 were available for ARSA enzyme analysis, and they did test all of those.

They came up with 20 infants who had low enzyme results on the ARSA, and then they subjected those to DNA sequence analysis, so that's going to be what's proposed to be the third tier of this newborn screening assay. Of those 20 infants, three of them had two ARSA variants, and the definitive MLD diagnosis.

Three of the 20 were detected to be carriers, and they identified of those three cases total that had

two variants, two of those were early onset, so the target that we're talking about, and the other baby was late onset, and they depicted that by genotype.

They went back and sequenced all 381 infants that screened positive on the first tier sulfatide, and out of that group they found three additional ARSA carriers. They found three SUMF1 carriers, that's multiple sulfatides deficiency, who those infants are expected to have a high sulfatide level, but they would also fall out on the ARSA enzyme analysis, so they wouldn't be necessarily picked up with the multi-tier test.

They also found four PSAP carriers in that second cohort, and three additional ARSA carriers were screened positive. And so, overall they used this three tier panel, and in this publication they also had a nice flow chart of the proposed screen. I just want to emphasize that screening is going to identify both the early and late

types, and so there are acceptable monitoring protocols and treatment for the late onset types, but programs will have to come up with a mechanism with their physicians to monitor for the late onset form.

Next slide. This is key question three again, another study that you've heard a bit about was the study from Dr. Gelb, Hong et al. in 2023 reported a validation, kind of a retrospective deidentified validation pilot study of 27,000 dry blood spots from the Washington program, and in this study using the first tier -- they used the first tier, only the C16:0 sulfatide. 1 in 140 babies screened positive for that part of the assay.

And then those specimens were also tested for ARSA enzyme analysis. They detected then one case of MLD, the genotype being identified two variants that have been reported in the literature previously, but because it was deidentified, they were not clinically confirmed in this retrospective pilot.

They also had newborn screening specimens from 40 MLD cases from around the world, and all 40 of them screened positive in their assay. So, then moving to the Bekri study, they did further investigation looking at using the multiple sulfatide test, using the C16:0, and the C16:1-OH forms of sulfatide, they tested a replicate set in the Bekri study of 592 samples for the multiple sulfatides, and along with other global newborn screening programs, who were using both.-- they combined their data.

And in the Washington study are the 592 samples. Zero of them screened positive, indicating that the C16:1-OH marker is the good marker, but you probably also would want to do both. There's other pilot studies ongoing around the world, and there's been cases identified in many other countries, particularly looking at high risk populations, presumably where there's an affected family member, and a higher risk for MLD than the population range. Okay. Next slide.

The New York ScreenPlus study thus far when I asked Joe Orsini for numbers, which was a little while ago when we were preparing these slides, we enrolled a total of 18,352 infants, 106 of those, and we were only looking at the C16:0, with a cut off there of .25 mmol per liter. If I back up to the Washington study they were using multiple median cut offs, so a little bit different cut off.

So, we did not have the ARSA enzyme assay available to us yet. It's not available in our lab, and Mayo Clinic is also working on an assay, and on a dry blood spot that they would use as a second tier. And so for ScreenPlus, we'd take the screen positive first two sulfatide baby samples, and we would subject them to DNA sequencing.

So, 106 infants were forwarded to DNA, so overall, 1 in 173 babies were positive on the sulfatide, and were subjected to DNA. Of those, one was positive, meaning it had a referral, meaning it had two variants

in the DNA, and ended up being a false positive, so kind of a small cohort so far. Next slide please.

Does the screening test have established analytic validity? We conditionally say yes. The Hanover study used accreditation from ARCHIMEDlife, this entity did a validation study on 500 random dried blood spots. They have five known MLD case screening Guthrie cards from known people with MLD. The validation study that they reported included the typical things you would do, and the analytical validity, analytical validation, which was carryover, cross-contamination, linearity, and limit of detection, lower limit of quantification and intra-run precision, inter-run precision and post processing stability studies.

There's also a proficiency testing program that's done via specimen exchange with a group in Manchester, and that Bekri study that I talked to is an international collaboration, looking at the 16:1 hydroxy. And from there, using the sulfatide, the

thought is that the rate of second tier positive is reduced about ten-fold.

Next slide. Key question five is are the characteristics of the screening test reasonable for the newborn screening system, among other aspects, a low false positive rate. So the proposal for this test is a three tier screen, so the first as I talked about was the MLD sulfatide screening, including the 16:1 hydroxy using LC/MS-MS. The second tier would be ARSA enzyme analysis.

This requires a gel cleanup, it's a sephadex gel clean up and a separate method LCMSMS to detect enzyme activity. So, basically you extract the blood spots. You clean it up using a gel step, then you incubate, and then you run it on the mass spec. So, it's a little more complicated than a typical mass specs in you know, through newborn screening, but the idea here is that it would be a lower volume of specimens going to that second tier, especially using the 16:1

hydroxy.

And then the last step would be sequencing of the ARSA gene, because this could give us information on the type of MLD that the family would have, and identify carriers, and that sort of thing. And that's expected to be fairly low volume, especially after the ARSA enzyme assay. Next slide please.

Continuing, some of the other things that we came across and discussed. The MLD sulfatide screening can be multiplex, along with Niemann-Pick-, Pompe, Krabbe, Gaucher, Fabry, MPS-I, MPS-II, and other MPS disorders, as well as Tyrosinemia Type I, and Adrenoleukodystrophy, and I underlined and starred all of the conditions that are currently on the recommended uniform screening panel, so some states are either doing all of these, or they're getting close to doing all of these tests.

You can also add Cerebrotendinous Xanthomatosis and Niemann-Pick Type C, and so you would

have a multiplex on the LCMS assay. Programs are leaning more and more-, especially with these types of conditions towards implementing higher tier testing to help improve specificity.

We talked a bit about yesterday about the Centers for Excellence, and the idea that there could be cross collaboration between programs. The ARSA enzyme activity can be done either internally within the newborn screening lab, if they choose to do that, or externally. And sequencing, similarly, can be done internally or externally, and states are working towards mechanisms to allow for these different tiers -
-- these- types of analysis to be done outside of their programs as well.

The condition is not necessarily a time critical condition that we have to transplant these kids within a few weeks of life, and if we look across the country we expect some are between 30 and 50 cases, and screening will identify like everything we do, a

spectrum of cases, but that's not as I said atypical for newborn screening. Next slide.

Is there widely available confirmatory tests or diagnostic process with CLIA and/or FDA approval as appropriate? The answer is yes. There are CLIA-approved labs that perform the confirmatory testing, so the confirmatory test is - is leukocyte ARSA enzyme analysis. -Urinary sulfatide concentration can be done either in a qualitative or quantitative form.

Qualitative is thin layer chromatography, and the quantitative form I believe is LCMS as well, and also DNA sequence analysis, if it's stage two is not to do that as part of the newborn screen, and do the first and second tier test only in house. We believe the number of babies who will need confirmatory testing across the country will be low, and there is no FDA-approved confirmatory test, which is typical of rare disease, as we all know, but at least, you know, we'll see where the LDT goes, and at that point we will have

to embark on FDA approval. Next step, next slide.

Number 7, are there defined treatment protocols for the condition when identified pre-symptomatically and treatment generally available? We say yes. There are expert consensus guidance documents, and there was a Delphi analysis on the management of MLD included in the nomination package. The Lenmeldy package insert has obviously step by step rules for the administration of the treatment, and as you heard from Mr. Suhr, there's also qualified treatment centers across the country.

There's five or six of them. But we also need to consider the detection of MLD through newborn screening will make all patients eligible for disease-modifying treatment, but we have to be cognizant of issues as we've heard about related to insurance and traveling. That treatment may not be universally available.

And so, it's incumbent upon us to make sure

that we work as hard as we can to create a mechanism to allow that to happen because as we said yesterday, we really don't want to identify these kids for which a treatment is available, and then have it inaccessible to them.

Next, key question 8. Do the results have clinical utility, balancing and harms? We say yes. Of interest there was a retrospective report done in the United Kingdom. This was done after the approval of gene therapy. They collected 17 cases of MLD, and they reviewed their case records and found that only four of those 17 MLD cases would be eligible for gene therapy at the time of diagnosis, and that's because three of them had an affected sibling, as we heard, and then one other one was identified early and was asymptomatic at diagnosis.

All the other cases, the other 13 had more advanced disease, and therefore not eligible for gene therapy. The newborn screening pilots always use a

natural history comparator, and the therapy has some side effects, obviously, that's commonly seen with the administration of chemotherapy, which is needed for the gene therapy, and also complications with ARSA antibodies, and we see this in Pompe disease and other types of these conditions and therapies as well.

So, the side effects of the therapy are well-known and established. There was a study by Fumagalli reported in 2022. They had 29 treated patients, almost all of them I think were asymptomatic, and by asymptomatic they meant that their early symptoms were ---- fall into the early symptom category that had as an IQ greater than 70, and be- able to walk ten steps.

So, they treated asymptomatic, and people qualified who had early symptoms as I've just described. Two of the transplanted individuals died due to disease progression, and these were the ones that were symptomatic at treatment administration, and one died of

an ischemic stroke after infection, and they were sort of unclear as to the cause of death, but didn't think it was related to the therapy.

The remainder of the treated patients were alive and generally had preserved cognition and motor function, and they compared this to a natural history cohort of 31 MLD cases, and all of these individuals suffered the typical decline without treatment in the same timeframe. Next slide please.

Question 9, does screening identify those most likely to benefit from treatment? Yes. Screening will identify infants with MLD, both early and late onset, and noting early is the target for this. Early identification and treatment will prevent the development of symptoms. We've seen Giovanni's story here, and whether the treatment is gene therapy.

So, the late onset of forms tends to be a management watch and wait, and then a stem cell transplant, at least right now, like the standard of

care for late onset, and that's also outlined in those management guidelines that were submitted. To an extent the genotype can help predict early versus late. Basically an early onset case is a null allele where there's no enzyme activity, and the later onsets have residual activity.

And so, genotype and enzymes levels also can help predict what type of MLD is present. And improved outcomes have been reported in the literature, and as described in this presentation. Next slide. So, the key questions summary is listed here. I'm not going to read over it. The answers in this nomination package satisfied almost all of the key questions that we had.

And so, we -- --our recommendation is that we should move it to evidence review. Thank you.

Committee Discussion

DR. CALONGE: Thank you, Michele, and thank you Chanika. I'll now open the floor for questions and

comments from Committee Members. Carla?

DR. CUTHBERT: Thank you both for your presentation. I have a comment and a sort of a question. The comment is just to let you know that at CDC we are working on our own methods for the sulfatide, and for the enzyme assay, and we're also working at developing reference materials as well, so again, this is something that we routinely do when conditions are being routed through this particular process, so that we get a head start. It takes a long time to get it done.

But just to let you know where we are with respect to that. The question is for Michele, you said that with your, with the assay that you guys are using the C:16?

DR. CAGGANA: Yes.

DR. CUTHBERT: For the first tier test, and that resulted in a number of screen positives, and we're just wondering whether or not you guys are considering moving to the 16:1 hydroxy, it seems to be a better

performing biomarker?

DR. CAGGANA: Yes. The New York screen plus study has been ongoing for a little while, and so we started off doing the 16:0, but we have some internal standard for the 0:1, and we're working on adding that to the ScreenPlus as well.

DR. CALONGE: A couple of quick questions. So, Michele, with the false positive that you generated from ScreenPlus, would that have not been a positive with another screening strategy? And what was the fate of that false positive?

DR. CAGGANA: So, my understanding is that it was referred for MLD. So the way ScreenPlus is a little bit different than the way we specifically do newborn screening because they're all from a single center, and so we made the referral based on the finding of two variants in the ARSA gene. I think one was path, and I believe one was a variant of uncertain significance.

And so, we made the referral based on that

result, and then they go to Dr. Wasserstein, and then she does the enzyme activity after the fact, and so that's when it was deemed to be a false positive. So, in a true --- if we do the three tier-, my gut is that we would not have referred that baby.

DR. CALONGE: Because the enzyme activity. --

DR. CAGGANA: Right.

DR. CALONGE: Do you know if in the Hanover study or somewhere else, whether ARSA carriers were notified?

DR. CAGGANA: Notified?

DR. CALONGE: Whether the results were returned?

DR. PHORNPHUTKUL: I don't believe so. In the literature, in the paper.

DR. CAGGANA: I think it's in there that they didn't, that they were not eligible to be reported, or something like that, so. Thanks.

DR. CALONGE: Other questions? Ash?

DR. LAL: Just seeking a clarification. So during the screening, the second tier where the enzyme, I think that's enzyme quantification, right? Where it comes to retesting the enzyme activity. Is that correct to say?

DR. CAGGANA: You incubate with an internal standard, and that you use to compare the product to, and so you're looking at an enzyme activity, but you're looking at it in a dried blood spot. The confirmatory test is in whole blood, so looking at essentially a leukocyte activity for ARSA on the confirmatory test.

DR. LAL: Okay. So if then three tier strategies - you- claim that as a confirmatory, the three steps together, or is there a need for further confirmatory testing after that?

DR. CAGGANA; It would be like anything we do, it's going to be further confirmatory test, and so the confirmatory tests are the leukocyte ARSA activity, urine sulfatides, and then if it's not done previously,

depending on how the newborn screening program operates, you would do the DNA sequencing as well, so it's another panel of confirmatory tests.

DR. CALONGE: Melissa, online?

DR. PARISI: Thank you, can you all hear me?

DR. CALONGE: Yes.

DR. PARISI: Great, thank you. I just wanted to inform the Committee, and those gathered that the NICHD at National Institutes of Health is actually competing a pilot study for metachromatic leukodystrophy screening among our pool of pilot states.

The proposals are due August 16th, and we anticipate issuing a task order award by the end of September. We don't know if there will be data generated from the pilot that will inform this nomination, but we're certainly trying to support pilot screening within the U.S. in a prospective manner to help support the nomination as well.

DR. CALONGE: Thank you, Melissa. At this

point I'd like to turn to our Organizational Representatives for any questions or comments. Sabra?

DR. ANCKNER: I just have a really technical question. How long are families going to need to be at this, one of the five centers for treatment? How long are we talking? I mean, you know, how long of the course of induction chemo?

DR. PHORNPHUTKUL: I'm not sure.

DR. LAL: Would you like me?

DR. PHORNPHUTKUL: Yeah, that would be helpful.

DR. LAL: Extrapolating from conditions that have been treated by lentivirus-based gene therapy, there is a --- the- time commitment is divided into two in general. The first is to do the autonomous sense of collection that are then used for gene modification and drug production.

The second is the admission is required for the actual stem cell transplant. So the transplant that

requires a certain duration of staying in the hospital, but after there are a few months that the families ask to stay within a really short distance of the treatment center. So, the total time commitment the second time could be close to four months possibly.

DR. ANCKNER: Yeah. So I just think it's important to just note that when thinking about how we're paying, it's not just the drug and the travel, it's the caregiver and family at one of five sites for months, which is great, but also expensive, so.

DR. CALONGE: Thanks, Sabra. Scott Shone, online?

DR. SHONE: Thanks. Scott Shone from ASTHO, or Org Rep from ASTHO. So Michele, I just wanted to on your slide, you had --- on one of your slides you talk about multiplexing screening for MLD with a variety of other lysosomal disorders, and other disorders. And so, I just wanted to confirm that the screening method because maybe I sort of conflate different things on

this, is that the marker for this is not part of a current FDA-cleared test, right? The initial- screening marker?

DR. CAGGANA: In an FDA-cleared test? No. Not yet.

DR. SHONE: Okay. So, thanks. And I just want to because of Michele's comments earlier, and then hearing all the comments during the public comment, I just want to draw your attention to the fact that MPS1, Krabbe, Pompe, ALD,- Tyrosinemia- Type I, are currently part of an FDA--cleared kit that many states use, including my state. When you add a noncleared target to a cleared assay, you then make- the entire test an LDT, a laboratory developed test, which would be then be subject to the concerns that were shared earlier.

And so, I'm not saying that that necessarily impacts any of this, other than to say this is a new barrier that is being --- and I wanted to put a sort of real world example to it, of here is a very robust

presentation by our colleagues on the Committee about this disorder, but the method that we need to use in any laboratory is not FDA--cleared, and can impact already existing FDA cleared tests that are finding babies across this country with conditions.

And so, I just wanted --- forgive me for getting on a soap box, but I don't want to miss the opportunity to bring an example of the real world impact of the new final rule on existing tests, as well as our decisions, and how we proceed with tests for disorders coming down the pipeline. -Thank you.

DR. CAGGANA: Yeah. I think we had the same issue with GAMT deficiency and some of the others, so yeah. We're, yeah, thanks for putting that out. I forgot to mention that.

DR. SHONE: Right. GAMT and MPS II, two recent additions to the RUSP that many of us with RUSP alignment legislation are currently trying to add in this new regulatory environment.

DR. CALONGE: I see no other hands, no other comments or questions. I wonder if I could ask either Michele or Chanika to make a motion?

DR. CAGGANA: I'll make a motion to nominate MLD for evidence review, to move MLD into evidence review.

DR. PHORNPHUTKUL: I'll second.

DR. CALONGE: Is there a second, and Chanika seconded. If there is no further discussion, I'd like to ask Leticia for a roll call vote, noting that Christine Dorley has recused herself.

COMMANDER MANNING: Noted. From the Agency for Healthcare Research and Quality Robyn Sagatov?

DR. SAGATOV: Yes.

COMMANDER MANNING: Michele Caggana?

DR. CAGGANA: Yes.

COMMANDER MANNING: Ned Calonge?

DR. CALONGE? Yes.

COMMANDER MANNING: From the Centers for

Disease Control and Prevention, Carla Cuthbert?

DR. CUTHBERT: Yes

COMMANDER MANNING: Jannine Cody?

DR. CODY: Yes.

COMMANDER MANNING: From the Food and Drug Administration, Paula Caposino?

DR. CAPOSINO: Yes.

COMMANDER MANNING: From the Health Resources and Services Administration, Jeff Brosco?

DR. BROSKO: Yes.

COMMANDER MANNING: Jennifer Kwon?

DR. KWON: Yes.

COMMANDER MANNING: Ash Lal?

DR. LAL: Yes.

COMMANDER MANNING: From the National Institute of Health, Melissa Parisi?

DR. PARISI: Yes.

COMMANDER MANNING: And Chenika Phornphutkul?

DR. PHORNPHUTKUL: Yes.

DR. CALONGE: Please note that the motion passes unanimously with one recusal. And so the MLD will move on to full evidence review from the evidence review group. I would also remind us all from yesterday that this also initiates the process for the public health assessment, and so, we'll be working with Jelili and APHL and the ERG to start collecting information necessary for that assessment. Any further questions?

I -- do we want to take another break, or do we want to move ahead?

Naming/Counting Condition ACHDNC Ad Hoc Topic Groups (ATG): Updates and Next Steps

DR. CALONGE: Let's move ahead if we have our presenters for the next presentation, which is going to be Naming Counting Conditions. It's going to be Susan Tanksley and Susan Berry. Susan, okay if we go ahead without a break?

DR. BERRY: Yes.

DR. CALONGE: Sorry. Just some -- by-way of introductions, Susan Tanksley is the Deputy Associate Commissioner and Deputy Laboratory Director for the Public Health Laboratory Division at the Texas Department of State Health Services in Austin.

Dr. Tanksley oversees public health laboratory informatics, grants, legislative affairs, and special projects. She has served on the Advisory Committee for Heritable Disorders in Newborns and Children, as an Organizational Representative for APHL since 2013, and has served as a member of the Evidence Review Workgroup for the Acting since 2012.

She received a Ph.D. in genetics from Texas A&M University in 2000 and has been certified as a high complexity laboratory director through the American Board of Bioanalysis since 2005.

Dr. Sue Berry is an Organizational Representative for the Society for Inherited Metabolic Disorders. She's a Professor of Pediatrics at the

University of Minnesota, and a member of the Division of Genetics and Metabolism. She's a Fellow of the American Academy of Pediatrics, and a founding Fellow of the American College of Medical Genetics and Genomics.

She is a current President of the Society for Inherited Metabolic Disorders, and a member of the Boards of Directors for the National Organization for Rare Disease, and for the National PKU Alliance, and is currently PI of their PKU patient registry.

So, I welcome you both and am pleased to listen to your presentations. Thanks, Sue.

DR. TANKSLEY: Good morning and thank you to the Committee for allowing us to present our updates from the Ad Hoc Workgroup on Condition Counting. Next slide. So many years ago, the issue of counting conditions and naming conditions came up very soon after the ACMG put together their panel of recommended conditions. And so, this has been an issue for many, many years, and what happened during that timeframe, so

after the ACMG panel, and even prior to that is there's this competition that developed between public labs and private labs.

We don't have that tension anymore now, thankfully, but we do continue to have this inconsistency in how conditions are listed on newborn screening panels, and the numbers that result from that, so how are they actually counted? Next slide.

And so why does this matter? So this is a snapshot taken from three different websites across looking at five different state newborn screening panels, and just even within a state there can be inconsistency in how many conditions are listed as being screened for. So, this causes confusion. Next slide.

And so, even though there may not be an actual disparity that exists, it can appear that there are differences in conditions that are being screened, and this is both in the number of conditions, as well as how they're named, and so this can lead to that

confusion, and not just across newborn screening programs, but with the public itself, and what is the state actually screening for, and how do you compare across states?

Next slide please. So three years ago, APHL and the newborn screening community recognized that this was an issue, and so an original taskforce was formed, and we had two primary goals.

One was that we identified that we really needed some guidance on defining what does it mean to screen for a condition, for the simple purpose of harmonizing our numbers in how we count. And then secondly, we wanted to improve that uniformity and being able to understand what's being screened for in one state versus another, just to say we needed consistency in what the conditions are named as well. Next slide.

And so, our original condition counting taskforce came up with some recommendations, and we presented these at the Newborn Screening Symposium in

2022. And so, we developed some rules around counting, and so those original rules that we developed were, the first one was really about what does it mean to screen?

And so, we spent a lot of time trying to define what screening was, and we based that on intent. It's the intent to identify a condition. So, when you screen you're looking for something, but you also pick up many other conditions as well. And then we also realized that when you screen for a condition you're not just picking ---- again, you're- not picking up just that one condition, but there is the spectrum of severity across all conditions.

And if you think about PKU, of course, the original disorder that was screened for, you realize that because you're screening for an elevation of phenylalanine, you're going to pick up a complete spectrum from classical PKU, all the way down to hyper phenylalanine -- goodness that's a hard word to say. And so, there's completely benign, all the way to

classical PKU, but that's where cutoffs are, and that's how we determine screening programs, what is it that we're trying to screen for, yet we're- going to pick up that entire spectrum.

So, we decided that we want to count phenotypes or clinical consequences as one condition, even though the spectrum of severity, and so those were our two main rules that we developed, and we presented at the symposium. And we also at that time started talking about nomenclature, and how would we actually recommend the changes in nomenclature.

So, we presented this information at the symposium, and then immediately launched a survey to anyone in attendance at the symposium, and then it also went out via listserv. And so, what came out of that survey was that in order for any state to adopt the framework, they said it would have to be endorsed by the Advisory Committee.

And so, we continued to discuss this, and

then, next slide, in May of last year I made a public comment to the Committee, and these were the three main recommendations as a spokesperson for the Workgroup as to what we were suggesting. And so, we wanted to first of all remove all references to secondary conditions from the Recommended Uniform Screening Panel, in recognition that most of those conditions are on that spectrum of severity.

And then we wanted to update certain core RUSP condition names and groupings based on the current knowledge of the condition, so much has been learned since the ACMG made their recommended panel, which then became the Recommended Uniform Screening Panel. And so we really -- we suggested at that time to update the core RUSP condition names and groupings based on the current knowledge.

And then finally, we advocated for the adoption of these recommendations by the ACHDNC because that is what would be needed in order for states to

actually make the changes. Next slide.

In response to the public comment, thankfully, it was decided to develop an Ad Hoc topic group to address this uniformity in counting, and so we are very thankful for that. And APHL, as part of their New Steps grant received a task order in order to coordinate this topic group. Next slide.

So this is a list of all of the Ad Hoc topic group members, many of whom were on the original task force, and we want to thank every member who has been a part of this, whether it was part of the original group, or the Ad Hoc Topic Workgroup. We also want to thank our federal partners who participated in the discussions.

We want to thank the Hemoglobinopathy Lab Workgroup, and particularly Dr. Cathy Hassell, who met with us recently to talk specifically about hemoglobinopathy groupings, and nomenclature, as well as endocrinologists, Dr. Ernie Post and Dr. Natasha

Heather, who met with us specifically on the endocrine disorders.

And we tried to put together a diverse workgroup, representing different parts of the newborn screening system, so that we could capture concerns, comments, and different perspectives. Next slide.

So, our group has been meeting since last summer, and thankfully, we were able to meet mostly in person. We did have a few who met via hybrid for our in person meeting, which took place at the end of June. And it was great to be able to have us together in person and be able to dedicate a full day and a half to really coming up with what are the final conclusions, and our coming together on expert advice that we could bring to the community today. Next slide.

So the first thing that we present to you today is how we are defining intent to screen. And so, what does it mean to actually screen for a condition? And so, our input is that a newborn screening program

should say it's screening for and list a condition on its panel only when the screening process is optimized to identify the particular condition.

And then we said well, of course, we're going to have to define what optimized means now, so next slide. So, what does it mean to optimize? And this is where it really comes down to, what is it that you're screening for, how do you modify all the parameters of your screening algorithm, so that you are truly identifying most of the conditions?

All of it is a great algorithm, but it's not always possible, and so we said that optimization of the screening algorithm involves modifying those parameters, so that sensitivity is balanced with an acceptable rate of false positives. What is acceptable? That's going to be defined by each state's screening program, and the specialists that it works with.

And if there are cases that are not identified by screening, each of those needs to be

investigated. We need to determine can the algorithm be changed? What's the impact of changing the algorithm, and if it's acceptable, then we should also modify the algorithm, so that we could pick that up, but those are decisions that have to be made each time there is a false positive reported --- sorry-, a false negative reported back to the program.

We all know that there are false positives with screening, and that's a consequence of trying to avoid the false negatives. So, optimization of a screening algorithm involves this happening repeatedly, and so continuously assessing and making adjustments as needed.

Laboratories need to receive the screening outcomes in order to do this, and this is all in as a part of the process of improvement in the laboratory. Next slide. I'm going to turn this over now to Dr. Susan Berry.

DR. BERRY: We each argued about which was

the hard part, and we each decided that we got the easy part of this discussion for ourselves, so thank you, Susan, for going through that because it was a long and really interesting process to do this with a tremendous amount of input, and I hope I can do justice to help describe some of the specificity and ideas that we came up with.

So, we ended up determining that defining the phenotypic spectrum would be really important for how you decided how to enumerate or count, and we wanted to present the concept that a condition should be only listed and counted once, even when a spectrum of severity for multiple subtypes. So for example, for LCHAD and trifunctional protein deficiency, they're both identified by identical --- by an identical metabolite-.

You cannot tell them apart on a newborn screening assay. You require follow-up diagnostic testing to do that, and so we should list and count both of those as a single, and in this case, attachment

disorder. They are clearly different conditions. -We understand and acknowledge that, that you will not be able to separate them on newborn screening, and so it should be counted as one.

Laboratories should, however, indicate when their algorithm can be optimized to detect other types of phenotypes, and so for example, when we're talking about Krabbe, if some people are deciding they want to watch for children with Psychosine levels between two and ten, which is you know, the recommendation was ten and the cut off is two, to identify infantile Krabbe.

Some programs will wish to identify those children with the lower range Psychosine. They can do so if their laboratory is optimized to capture those children also specifically. Similarly, with for PKU, right now our list is two disorders to call it classical PKU versus hyperphe. It's really a spectrum disorder, but if you optimize so that you are going to pick up hyperphe and identify it, then you can count it

separately. Next slide please.

So, with regard to the secondary conditions, which is part of the bone of contention for all of us, and a source of complexity in our Recommended Uniform Screening Panel as it now stands.

And in this case the recommendation that our group arrived at were to apply that phenotype spectrum rule to group or rename certain of the core conditions, and then ensure that any related conditions not named on the RUSP, are listed in their differential diagnoses or detectable disorders that can be found in information such as the ACT sheets for each of the RUSP conditions.

So, that means that some of the disorders that we currently list as separate conditions, as even core conditions at this point, would be it's not that they won't be reported or detected, it's that they won't be listed for counting purposes. It doesn't mean that we're going to stop looking for them, it means that we're going to be more uniform in how we understand our

reporting of that group of metabolites for example.

We're going to ask the Committee to consider the option of reviewing the conditions that are on the secondary list, so that we can decide if they should be added to the core conditions. There are some that probably deserve that. There are some that we should just make go away.

You all know who they are. I won't say any names, secret names. All right. And so, we should also remove the designations between core and primary and secondary conditions, just so that there's one list of conditions that is Recommended Uniform Screening Panel because I think it's only been a source of confusion, and distress to have this distinction.

Next slide. We wondered if it was worth having a standing workgroup, or some strategy by which we can think about removing conditions, as well as which conditions can be removed. And that's --- we'll come back to this in some of our summary questions. Thank

you. -Next slide.

So some specific conditions, and we can kind of give you some information, and there are probably going to need to be some clarifications of an explanation of what we were thinking through because it took us -- we went round and round about this for quite a while, so it seems familiar to us, but it takes a minute to absorb it when we are upending what the previous recommendations were, so next slide please.

All right. Now, one of the things we are suggesting is that there will need to be a regular review of the names to make sure the nomenclature matches, and so for example we suggest that we should align the naming with the currently recommended nomenclature for disorders.

So for example, when we list what is now referred to as PKU on the panel, the American College of Medical Genetics has actually suggested that this condition be referred to as phentolamine hydroxylase

deficiency, and so we would recommend that that nomenclature be used instead of calling it PKU.

It doesn't mean we're not respectful of the long history of what PKU is and how it's been improved by newborn screening, it means that we're acknowledging the advances in science that have brought us to this point. Beyond that, when there isn't a specific recommendation along those lines, we may use the disorder name based on biology or phenotype, so for example, tyrosinemia type I, or Pompe disease rather than necessarily using an enzyme.

When multiple enzymes can cause the same condition, the disorder who is our target, and remember, we are talking about what you're screening for, as opposed to what you detect, right? So methylmalonic acidemia caused by methylmalonyl co-A mutase deficiency is the target.

Galactosemia caused by GALT deficiency is the target. Homocystinuria caused by cysts finding beta

synthase deficiencies, the target that should be identified in newborn screening, and congenital edema hyperplasia, we understand there are multiple forms, we're not saying that won't be detected, by the target is CAH caused by 21 hydroxylase deficiency.

And when the analyte used may detect multiple underlying causes of a single phenotype, you should list the phenotype as the condition, so the best example of that is possibly SCID. Yes, the target was actually SCID, but it really identifies a broad spectrum, T cell immunodeficiencies.

But what you're trying to do is identify those severe combined immunodeficiencies, and you will detect other disorders by using that strategy. Next slide.

We had a very productive conversation with our colleagues who were expert in hemoglobinopathy, and the recommendations that they offered to us would be that there would be four conditions that encompass the

conditions and phenotypes, genotypes and phenotypes in our table, and these would be we would list sickle cell disease, which would encompass a variety of genotype, phenotype, genotypes.

Alpha-thalassemia, which again includes a group of genotype phenotypes. Beta--thalassemia-, and then we fully acknowledge, and they understood and recommended to us that you name those three specific conditions, and then group the other differences as clinically significant variant hemoglobin.

And what we would say is that optimization, once again a key element in this, will be necessary to list, and other clinically significant hemoglobin allows a state to list the possible genotype phenotypes, as a single condition, and thus simplify their strategies. It doesn't mean they don't detect, it's what are you screening for. Next slide.

So for example, for galactosemia, this is sort of an example that help people sort of gather what

we are trying to do. If you're using a first tier test that looks for both the GALT enzyme, and total galactose, programs can actually list two conditions because they will have two sets of conditions if they optimized.

They will be able to detect galactosemia due to GALT deficiency, and non-classical galactosemia, which includes the variant forms of galactosemia. Now, those states that do not use galactose, would only be able to list, and should only list galactosemia due to GALT deficiency, so this is to follow our definition of optimize.

Next slide. For congenital hypothyroidism, most of you may be aware that some states use T4 as a first tier, some use GSH, and you get a different spectrum of disease in this, and so states that use first tier, with the intent to detect central hypothyroidism, via TSH, then they can list two, because they can optimize for both primary and central

congenital hypothyroidism.

Those states that use TSH primarily may have a different ability to list. They're not going to necessarily pick up central hypothyroidism, and should not list it amongst the conditions that they detect. Next slide.

So we had --- we did a list of questions that we hope will provide a forum for discussion, and I'll briefly go through these, and then throw this back to the team here. We wanted to really consider in thinking about the differences between a condition we're screening for, as opposed to one we may detect, what was your target, we often bring this up-.

But this has been a point of contention for a long time. What was your target? What were you trying to screen? And what role will optimization play in decision making about screening versus detection, and how they're listed? So the community will want to consider that set of issues.

We hoped that the Committee might be able to agree that a condition should only be listed and counted once, even if a spectrum of severity or multiple subtypes exist, again to simply and uniform, make more uniform condition counting and to make it clearer to the public and to our constituents, what we're actually trying to accomplish with newborn screening.

Now, in considering the nomenclature, we wondered if -- would our nomenclature rules provide better clarity for the intended targets, and could we have standard procedures to facilitate that consistency to support states in making these adjustments. Next slide. We had a lot of questions for you.

So, is there utilities still in distinguishing these core versus secondary conditions, and what are the risks and benefits of doing so? That requires, I think, some thoughtful analysis. Is there sufficient evidence to swap some people, some conditions that are currently on the secondary list to the core

list, and again, and the purpose of modifying and unifying our list into a consistent, and understandable group of conditions.

And finally, would there be mechanisms by which the Committee can establish procedures on how to remove conditions from the RUSP, and develop processes to determine which conditions might be removed? A touchy point that we've had difficulty talking about, but it's time for us to at least discuss it.

And with that, next slide. I bring it back to you. This was one of the most entertaining and frustrating experiences ever to be on this group, and it was such a valuable learning experience for all of us, particularly for me, to see, you know, to think it through and say how can we really make this better, and improve our communications and the effectiveness of newborn screening by thinking about what we call things, and being clear on what we screen for as opposed to what we detect, and with that I'll turn it back over to team,

and open the floor for discussion.

Committee Discussion

DR. CALONGE: Thanks for a great presentation. I wonder if we could --- sorry-, keep the slides up and go back two slides.

DR. BERRY: You want the questions?

DR. CALONGE: Questions that --- I don't remember them.

DR. BERRY: I understand. We spent a day on that, just the questions. Back two slides.

DR. CALONGE: It's slide 21. And as we get that up, Jennifer?

DR. KWON: Jennifer Kwon, Committee Member. I don't need the questions put up because I still haven't graduated from the examples. Can you walk us through --- so part of me keeps thinking that states are going to differently reoptimize, and I'm not sure how that gets controlled for, but I was wondering if you

could walk through your example of Krabbe disease, and particularly, the situation that I'm sure is going to come up that you know, the target was supposed to be the initially Psychosine- over 10, but how about states who have like a broader range?

How -- tell me again how that would work?

DR. BERRY: Let me make sure that I get this right, so I'm going to look at you as I do this. So for Krabbe, you know the recommendation by the Committee was to the screening target is infantile Krabbe, children who have low enzyme values, but the recommended second tier test that's part of the appellation for the condition with a Psychosine greater than 10, right?

And so, that's the target for screening. Some states who have initiated screening, other than some --- that was on the RUSP, use actually and report the results of children who have Psychosine between two and ten. And they feel that they can with confidence identify those as children who have a meaningful

condition that will merit ongoing -follow-up-.

Those states that have optimized their testing strategy to identify the children with those lower Psychosine levels, can realistically count both infantile Krabbe and other Krabbe subtypes that would be identified by those lower. So, they would have two things, they would have infantile Krabbe, the target recommended by the recommended uniform screening panel, and they, as you know, there are states that just identify things that aren't on the panel, and that would be one.

That would be something, and they could count and enumerate it. We want to know what people are doing. We just want to know to have them do it consistently. Does that reflect it?

DR. KWON: Yes.

DR. BERRY: I'm just looking around for other Committee members to make sure I don't screw it up.

DR. CALONGE: Jeff?

DR. BROSCO: Just a quick question, a clarification of that. So, does that mean that the lab is doing two different optimizations, one for Psychosine above ten, and second from two to ten? Because I thought that was the optimization, and that was one condition, two optimization.

DR. BERRY: They would have to be able to demonstrate that they had optimized their assays to identify those children between two and ten, and the case of Psychosine if they only have I think very good Psychosine assay, either by their self-performance, or by where they send it, then yes, they could consciously say we have optimized both, and so we can identify both.

Other states may never accept or want to know the results between two and ten, they couldn't claim that they are identifying children with these variant forms of Krabbe. They would have their target for infantile Krabbe, which was the Recommended Uniform Screening Panel addition.

DR. KWON: Do you think it's likely that states are going to optimize --- I guess I would imagine that states would say we're looking for Krabbe disease with a Psychosine of greater than 2. I mean I think -- ---

DR. BERRY: If they're doing that, then they're looking for more than one form, and they would definitely be identifying more than one form of Krabbe, and they can say they were.

DR. KWON: Okay. Okay.

DR. CALONGE: Carla?

DR. CUTHBERT: So, I really like what you guys were doing, but I started getting a little bit of anxiety.

DR. BERRY: Oh, we did too. So, join the club.

DR. CUTHBERT: Only because I'm thinking about Homocysteine - Cobalamin.

DR. BERRY: Very good question. We were

hoping someone would ask us about that.

DR. CUTHBERT: So, I can see a spectrum, and then I can see, you know, there are a number of vitamin deficiencies that if you have internally a series of second tier tests, or other sort of testing in your algorithm, in your state lab, to evaluate those, again as a biochemical geneticist that causes me a lot of excitement, but I'm just thinking that you -- we will have programs with smaller lists, and programs with longer lists, you know.

DR. BERRY: Well, so we have two things. We have the Recommended Uniform Screening Panel and what's on it, and then we have what states do, some of which are tied to the RUSP, some of which are how should I say,- free range, okay. And there will be discrepancies in what states do. We acknowledge that. But what the Committee acknowledges as being on the recommended screening panel, and what states do with that, plus, are two different things I think. So, will there be

still- asymmetries in what states do?

Yes. That's not changing. You're not going to get everybody to only do what's on the Recommended Uniform Screening Panel, that's not going to happen. We don't expect that.

DR. CUTHBERT: I like the clarity that you're talking about, and the way that you define what you're looking for, but I still feel a level of anxiety. Excitement, but anxiety.

DR. BERRY: What you're going through is exactly what we did as we were working on it, which is we had to think it through step by step. And as we did, we felt more and more convinced that the path we were following was attainable, and realistic. But you have to think it through.

So, you asked for example, about the Cobalamin disorders. So the target is methylmalonyl coA mutase deficiency, methylmalonic acidemia. You will likely detect other children with Cobalamin forms of

those disorders, Cobalamin A and B. I would argue that the current strategy by which we identify- these ineffectively detects those, misses a lot of them.

And we probably shouldn't claim we're screening for something because we can't -- it's very difficult to optimize assays as they currently exist for Cobalamin A and B. It doesn't mean people won't try to detect them, and won't report them, but they won't be included as screened conditions that would be detected conditions. Does that make sense?

DR. CUTHBERT: Okay. I like the intent, and I like the intent is to identify pretty much as many as -- I was going to say as many as you could.

DR. BERRY: Yeah.

DR. CUTHBERT: But identify all the cases.

DR. BERRY: But it helps programs to not end up being in a position where they claimed they could detect something that they really aren't prepared to do because they didn't optimize for it. Their strategy was

designed to pick something else up, and by golly, you detect this also. And so, you will detect it, you will report it, you will do your best, but you're not going to find every case of some of the detected disorders. Yeah, go ahead.

DR. TANKSLEY: So, we were blessed to have parent advocates on our workgroup, and their input was so valuable. So, their concern is that how do we know that our condition is like we just --- we want it listed somewhere, and so we felt that the ACT sheets were an appropriate place- to list because that has the differential diagnosis.

And so, the original intent in ACMG when they developed their recommended panel way back was that these conditions would be -- so the core conditions were scored, and those conditions made the core list, right, the 29, and then there were these other conditions that didn't quite score as highly, but actually could be detected when you were screening for a core condition.

At the same time, some conditions were elevated that aren't in the differential diagnosis, but because tandem mass spectrometry was being used as the screening method, if those analytes were detected and identified as elevated, where it would indicate a potential, then those were to be reported.

So, the original concept of secondary was targets, now conditions, was that those results would be reported. If they were identified. What we're suggesting is that we are screening for a particular disorder that we have optimized in order to identify. At the same time, we're still going to identify most of those conditions that are on the secondary conditions list now, and it's in the differential diagnosis that it will determine what is the actual diagnosis.

So, what we are proposing is that the Recommended Uniform Screening Panel, or a state's list because there are definitely states screening for things not on the RUSP yet, but that the targeted newborn

screening, what is it that we have optimized the assay to detect is what's listed.

And then those other things that could be identified would be listed on the ACT sheet as part of the differential diagnosis.

DR. BERRY: Again, we're not, not detecting, we're not turning off the detection possibilities. We're turning off the idea that you're going to list 15 things when it's what you're really listing is a differential diagnosis.

DR. CALONGE: Melissa? Melissa? Okay, Christine?

DR. PARISI: Sorry about that. Anyway, I had a question about counting, and first of all this is just an incredible amount of work, and I'm so impressed by what you all put together. And it's kind of a tour de force. But I was wondering about counting, and you know, the potential for grade inflation and counting inflation, which was one of the impetuses for this

activity.

And I'm just wondering if in the final count, if we could make some sort of recommendation that states, or programs indicate how many of the RUSP conditions they screen for, and then I mean I know this gets into a two tiered system again, and how many other conditions they screen for. If we eliminate that secondary category, but still have some sort of differentiation. Because I think there's still some value in understanding how many RUSP conditions a state screens for.

DR. BERRY: Yes. I'm not going to speak for everybody, but there's no way to get around the idea that different states screen for different things. That's not really changing, nor are we necessarily recommending that it do so. But I think an acknowledgement, if the Recommended Uniform Screening Panel is a certain set of items, that you acknowledge which states are able to, and have succeeded in being

able to screen for those.

And then they can certainly make sure that people know that they've chosen to add other things by whatever mechanism their state does that. There's going to continue, you know, some of those will be by statute. Some of those will be because they're a state newborn screening panel and the advisory committee added them.

I would recommend against states adding things that they're working up or trying. Those shouldn't probably be counted, but there's no way that we're going to make everyone screen for the same thing. That's not how it works. That's some acknowledgement. The goal is to get all the states.

That's what we're trying to do is get all the states to do all the things on the RUSP, we've just got to be clear what the RUSP is, what we're asking them to do, and then people need to know that their state can accomplish that, and whatever else states can do, more power to the states, good for them, that they can add

other things to help children.

DR. PARISI: Thank you.

DR. CALONGE: Christine?

DR. DORLEY: Really good presentation. I noticed the slide regarding counting conditions for hemoglobinopathies that beta-thalassemia, and alpha-thalassemia were listed. What other conditions from the secondary targets was the workgroup thinking needs to be reevaluated to maybe be- moved up to the core panel, and then would that take advocacy groups?

Would it be because these were already considered before, and put on the secondary target that they go immediately to evidence review? What's the mechanism behind it to re-evaluate these disorders, and then move them forward?

DR. TANKSLEY: Thanks for the question. So, first I want to emphasize that just because we listed four categories of hemoglobinopathies doesn't change what's on the Recommended Uniform Screening Panel. It's

a matter of defining, you know, what a state has optimized screening for.

So, currently the variant other hemoglobin are clinically significant other hemoglobinopathies is listed, so it's a really great question, and one that would have to be considered. We didn't think that far through it for hemoglobinopathies, but we did think that it's important because we have so many years of data at this point, that there may be conditions on the secondary list that are clinically significant, that there have been advances in treatment.

There's so much data now that there might be enough evidence to actually suggest that is a condition that states should screen for to be advanced to the RUSP versus a consequence of screening on.

DR. CALONGE: Ash?

DR. LAL: So I think the requirement for optimization, intent and optimization, that's a great start I think for considering whether or not a state is

screening for a condition. But I think if I thought there was something that could be added to your discussion and your workgroup is that what does a state do with the results, the screening result?

Is there an intent to follow up? And what is the path to that -follow-up? So, of course you can diagnose a condition, but does that initiate then some kind of a formal process to who is going to counsel family, and how the patient is going to be followed if the condition is a secondary conditions-, not the primary?

DR. TANKSLEY: So, correct me if I'm stating this wrong, please. So, add to the definition of the intent to screen that there's reporting and follow-up-.

DR. LAL: That there's intent to follow up-?

DR. TANKSLEY: Yes, yeah, I think we took that as a given as what screening means because we weren't looking at it as just the lab test, but the process. I agree, yes, there would definitely have to

be reporting and follow-up- on those in order for it to be listed.

DR. LAL: Yeah. I would think that it should be as formal as the process for optimization has been demonstrated.

DR. TANKSLEY: Okay.

DR. LAL: And has been demonstrated, but there should be I think in many of these secondary conditions, especially as you listed the hemoglobin disorders, many of them may not even perhaps need some follow-up, maybe not, but how does the ----- what's the communication pathway, and who has to bear the responsibility that I think we need to lay out, especially for secondary conditions.

And if you have both the intent and the optimization, and the follow-up-, then I would agree that that would be through the screening.

DR. TANKSLEY: So, you're suggestion is to add to our optimization process about the follow-

up- piece of that?

DR. LAL: I think that I would certainly think that's necessary for a condition to say there would be a screening or something.

DR. TANKSLEY: In order to list it, include the process of newborn screening, not just the testimony.

DR. LAL: That's my thought, yes.

DR. CALONGE: Michele?

DR. CAGGANA: Just a couple comments. And getting back to moving from the secondary to the primary, I think the example was put up for GALE and GALK, so they're on secondary now, but if you're screening for them it could be promoted to the primary list for a state. And then forgive me for bringing this up, but I thought we had Krabbe counted as a single condition, and then the difference of types would sort of fall under the severity, and be more explained in through the ACT sheet version?

DR. BERRY: There are details that we all need to be ironed out, correct.

DR. CAGGANA: Okay.

DR. BERRY: So, if I haven't made it clear, the whole point was that some states will clearly detect them, and they could acknowledge that.

DR. CAGGANA: Yeah, okay.

DR. BERRY: We can make sure that they will try to be consistent about them as well.

DR. CAGGANA: Yeah, yeah, I mean this whole process is sort of trying to give people a roadmap on how to categorize things.

DR. BERRY: Yeah. How to categorize things, and you know, that was I told you it was important that we were going to, you know, sort of plant someone in the audience about the MMA if we haven't had it brought up for example because that was one that was really confusing and difficult for us in the discussion.

DR. CAGGANA: Yeah. This was quite an

adventure, so thanks.

DR. CALONGE: So, I have a few observations and questions. I'm trying hard not to get in trouble. I really liked this presentation.

DR. BERRY: Try not to get into trouble?

DR. CALONGE: Because I have to work with them. I was just kidding. They're great partners and colleagues. I like what you put forward quite a bit, and I think the clarity could bring, and the ability to really talk about the RUSP as a more coherent set of uniform recommendations is important.

There's a Chinese proverb, call things by their right name. I like that. That clarity, that brings is very good. I think if you get to the original core, I've always talked about because I was there after it was approved. It did not go through evidence review, it went through a vote. So, I think getting rid of the phrase core conditions is a great idea.

And then I think having the RUSP be the RUSP

is also a good idea. Where I worry about getting into trouble is I know that the statute says you should have a secondary condition, I think we should move towards figuring out how to make that a null set. So, if there are no secondary conditions, you're still meeting the statute, you just created a null set.

And I think the secondary conditions that we should be screening for because of evidence of efficacy should go on the RUSP. I think conditions that we look at that don't meet the conditions, or the qualifications for at least moderate certainty of at least modern net benefit, at least to be considered, should not be on a list. I think that separation gets clarity about what uniform, sorry, Recommended Uniform Screening Panel really means, so I want to say I support that.

We've talked about before, creating the process, which we talked about in 2011. How to create a process to take things off, to re-evaluate and say should it stay on or not. I love the idea of a separate

workgroup that could do that because we haven't moved the ball very much further, but I think that's a great idea.

And I think one of the first things to look at would be the secondary conditions, what should be promoted, sorry, what should be part of the panel, and what should drop off the panel. I love your idea about nomenclature. I like that consistency. I don't care what you call it, it has to be something that we can recognize. There may have to be a translation table that exists for a little while, but I think we can get there.

Could you go onto the next slide? I'm just looking at your questions.

DR. BERRY: We actually made a table like that if anyone wants to see it.

DR. CALONGE: I think I covered all of these, so I think one of the things that would be helpful is for your group to at least continue for a while, and be

able to translate your recommendations into what it would look like, and what you think the names would look like.

What do you think --- where do you think we should start by looking at the secondary conditions, because it won't happen overnight, and thinking about a way to work through them in a way that says it's either on the panel, or it's not on the panel. The last thing is the two words, "expedited systematic evidence review," don't- go together, just so you know.

DR. BERRY: I know that.

DR. CALONGE: And so, I don't want to give the impression that that's an easy course, but I think it's something that could benefit the naming and counting of conditions, and helping parents and advocates understand what's being done state by state. So, those are all my comments for what they're worth, and I really applaud the work that's been done.

I have Jeff, and then Christine.

DR. DORLEY: Just a quick thought from you guys on what you think about this regarding this order on the core list that you don't have a really optimal analyte for screening. And I think back to Tyrosinemia Type I with Tyrosinemia being used for a long time until [inaudible] came along. So, homocystinuria is another example of an inoptimal analyte that's- used for screening, which would be elevated finding.

So, can a state really say that they're screening for homocystinuria when they are not "optimized" with a really great analyte to pick up that disease? And with the recommendation would you all recommend because I know CDC has a new assay that's been developed that is optimized for homocystinuria. How do you reconcile that and come to a balance?

DR. BERRY: Well, homocystinuria is one of the ones we actually had a long discussion about because the challenge in that one is that we have it on the -- it's a core condition, and we do a terrible job with

it. Terrible job. And it's kind of like the cobalamin disorders done at A and B. You probably will detect it, or some of them, but you don't detect many children with homocystinuria because we don't- have an optimized assay.

Should it even be on the panel, that's not because I don't want to detect it, it's just that we don't have a really ---- we're not doing a very good job with it, so one of the questions for some disorders honestly will be is do we have an optimized evaluation for that disorder, and if not, how do we accomplish it? Where does it belong on the panel if it's not an optimized one because I don't really think we want to promise that our programs are effectively screening for a condition that we missed so broadly. -

You know, it kind of a dirty secret I would say that we don't do a very good job with them, but it's true and everyone knows it. We don't do a very good job picking up kids with homocystinuria, you're kind of

lucky if you get them. So, is that part of our responsibility? Yes.

If there are disorders that we think that are so important that they should be a primary disorder, you better have an optimizable assay. So, that's my two cents personally. I'm not going to say it's everybody's job to do.

DR. CALONGE: Carla?

DR. CUTHBERT: So, I agree with you, Christine, but I also perhaps see the evolution of newborn screening being such that we have a biomarker that we think is good enough, and that we think we're picking things up. And then over time we realized well, this is not good, and here are the reasons why.

And I'm not sure about what the process ought to be because I think that the initial evidence review would have indicated that this is a valuable disease to detect.

DR. CUTHBERT: But a shift in the biomarker

may just be one of the quality improvements that's just inherent in the entire process, and just have that discussion, have that evidence. I don't know what the process would be, but just to have that discussion that we should move towards something that is better.

DR. BERRY: And I guess the paradigm for that would have been the tyrosinemia section in the last time issue because it was broadly acknowledged not very long after we started, and included it, but it was a terrible choice to screen for tyrosine. It doesn't detect most if many of the cases, you have a lot of false positives, it makes everybody crazy.

I spent many hours not having people with tyrosinemia that I worked up, and the response of the community was to improve that. I would hope that in this similar, like it's very parallel. I would hope that the Committee would acknowledge that there are ways to improve that assay, and work together to do so, so that we could responsibly say we were doing the

screening correctly.

DR. CUTHBERT: And if we say that this is just the normal path, I think that that would be pretty helpful in --

DR. BERY: Yeah. And the other thing is would you allow you to optimize for the other homocystinuria to really begin to think about how you look at low methionine as opposed to high methionine, another and missed opportunity that we have at this point.

DR. CALONGE: Jeff. Okay. Let me turn to Debra.

DR. FREEDENBERG: Thank you for the tremendous amount of work that is in thinking about how to clarify this. I have two comments. One is really more of a question, but it's a practicality. There are some states who provide clinical resources to children who have screened conditions identified in newborn screening.

And if you take those conditions off the

list, then that state will not be obligated, and may not provide any of the follow-up and clinical services for those conditions that are clinically significant. And so, I'm worried about a loss of resources for the clinical population, if it's- no longer considered on the panel, that condition.

And then the second thing I'm really struggling with is thinking about like Cobalamin C's where there are certain ethnic populations that have higher incidences, and there's some states that have a higher population of those ethnic variants. And so, I'm struggling in trying to figure out how would that be approached because it may be true with a state, and multiple states, and it may not be recognized, and it may not go on the condition list, you know, as a whatever it is, for the Cobalamin C's. So I'm really sort of confused about how that would be approached.

DR. BERRY: So, Cobalamin C was one of the ones we had a long discussion about because it's

certainly on the secondary condition, and I think we know a lot more about Cobalamin C than we do when we started. I would submit that there's a reasonable chance that that would be a condition that on the appropriate consideration, there are a significant number of children who benefit from identification that it would fit the criteria, and not my place to say this.

But I think it would be one of the ones that if you were going to move some that are on the RUSP, you'd move it up, move it up, move it onto --- it would become part of the core condition, as an example. Would states say they're only going to deal --- so this is part of our challenge in the paradigm shift we're suggesting, which is that just because it's not named as a condition doesn't mean you don't detect it as part of newborn screening, and states would need to acknowledge that in terms of service provision.

I don't know how to tell a state to behave, but the intent is not to not detect and not indicate the

importance of those findings. It's simply not to count 20 things when one will do. That's the only --- so I don't know how to fix that. It's a legitimate concern that we would have to address-.

DR. CALONGE: Amy?

MS. GAVIGLIO: Yeah, thank you. Amy Gaviglio, National Society of Genetic Counselors, and I have several comments. The first is to just kind of affirm what Dr. Caggana is saying as it pertains to listing diseases with the phenotypic spectrum such as Krabbe.

The Committee agreed that we would count it. It would be listed once, and with a caveat of whether you are truly really just targeting the infantile with that 10, a Psychosine of 10, or not, and that would hold true for things like PH deficiency as well.

I also really agree with this idea of, you know, removing a list of secondary conditions and deferring to the ACT sheets for several reasons, one of

which is Dr. Ostrander and I have spent years of our lives reading every single word and tweaking every single word of those ACT sheets, including keeping abreast of all of the differential diagnoses that may come from screening.

And if you look at the ACT sheets, the differential lists that we have are much broader than what is listed on the secondary, and so I do think that's a really great resources, which also speaks to my hope that they will continue on with maintenance because I really can't understate their importance.

And then my final comment is a bit, I'm just kind of cautioning us to in thinking about, you know, relying on this idea of evolution of screening and improvement, just simply in comparing it to the standards that we are asking new diseases to come in with, which are very high clinical and laboratory analytical values, and so I just would ---- it causes me hesitation of it to say oh, it's okay, you know, that we

don't have a great marker, it will evolve over time when we're setting such a high bar for those diseases that are coming in now, thank you.

DR. CALONGE: Thanks. Bob?

DR. OSTRANDER: Robert Ostrander, AAFP. I have two comments. One is this was terrific. And dealing with the sort of secondary conditions and additional findings is something again that we deal with all the time in clinical medicine. I mean we were -- again-, I take care of a lot of adults, and you know, we always order a CT for one reason, and finding another, finding something else.

And then we act on it, but we don't expect that CT for abdominal pain to be a good screening test for ovarian cancer. Although we stumble on it sometimes, and that is the same principle that exists here. We're screening for something. We come up with a condition, and yeah, we need to act on it when we find it, but if we start holding the screening test to

finding all of those, then we're going to shoot ourselves in the foot and never complete anything.

So, I think this is not new. You know, this is not a new concept that we stumble on things that we have to act on, and we need to report them, but we can't get ourselves all wrapped up in trying to then make it a perfect test for that too.

My second comment, you know, just follows, you know Amy's about our advisory group. Not only do I hope and think we need to be continued you know, I think the switch over, and is both an opportunity and a threat.

We've lost some continuity on the threat side, but the opportunity that if it's more under this HRSA umbrella, it may allow for better coordination with your group, and the ACT sheets, and that's going to be critical if we're going to rely on the ACT sheets as a component of what you're going to include and what you're not going to include in the nomenclature piece of

the whole thing.

And I'm sitting here looking at the hemoglobinopathies, and you're not going to make all of the diagnoses match because the ACT sheets are for other things. They are for some of these incidental things. I mean I've got like 5 alpha-thalassemias, and you know, Amy will tell you.

We did hemoglobinopathies in the thyroids at the end because the different tests and stuff, we've got different ACT sheets for the same screening condition because of that, so I suggest that as you work forward with whatever reconstitution of the ACT sheet workgroups you create, that there be a combined advisory committee where the two committees talk to each other fairly regularly to achieve the goals that we discussed today.

DR. CALONGE: Thanks, Bob. Natasha?

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance. First and foremost I want to say thank you to the Committee that has cleared worked, our ad hoc group,

that has worked so hard on this. This is something that we've been talking about for a very, very long time. I was just remembering that one of my first conversations with Ken Pass, taking it way back, was about so why is it different?

So that was a long time ago, and but this is really, there's a bit of a culture change here, and that takes time, and the good thing is we've been talking about it for a long time, so we're like halfway through that generation that usually takes for big things like this to change. So it's good, it's a positive.

I will also say that, you know, my heart has kind of been racing thinking about, how do we even start to communicate this to parents. Like really racing. And so, I know yeah, give me the paddles. So, I really hope that as this group is you know thinking about the next steps, in terms of nomenclature, and potentially cross walks around that.

We're also thinking about having a similar

type of effort on the true communication and education side, that it's not just post up these charts, and then the education is done, no. It's really just going to be beginning. And so, I really hope that whether it's the constitution of this group, or a different group with different experts around communicating to families, and the public, because I know you had parent advocates, and that's great, and we're glad that some of our parent advocates are on that.

But that's one lens. That's a different lens than the public, which is a different lens than the media, who will want to construct things in a certain way so again, thank you for all of this effort, and I hope that there is the ability to support the efforts that will need to come after this in the implementation phase.

DR. CALONGE: Of course, Scott?

DR. TANKSLEY: Sorry, can I response first?

DR. CALONGE: I'm sorry.

DR. TANKSLEY: So, thank you Natasha. When we had our in person meeting we spent about a half a day on starting to think about communications, and we didn't present any of that today because we wanted to present our ideas to the Advisory Committee because we really need responses to know what we are going to communicate, but we've talked about communication to newborn screening programs.

We've talked about communication to legislative bodies. We've talked about communication to parents and the public, and I'm probably missing something else, but we have brainstormed what are all the things, and all the bodies that we are going to need to communicate to once we have guidance from the Advisory Committee.

And thank you because you were the first person two years ago when I presented at the symposium who said how are you going to communicate this? And how are you going to get that buy-in? So, thank you. Yes,

you are.

DR. BERRY: That was actually the most --- it was the most exciting part of our discussion was how could we help people realize how this will improve and inform newborn screening in positive ways, and that's I think one of our critical sales items, is that we have to talk about how this makes newborn screening better for everyone.

DR. CALONGE: Thanks, now Scott?

DR. SHONE: Thanks. Scott Shone, ASTO. So, I agree completely with the conversation that just happened with Natasha and Sue and Susan, you know, but I don't think that the communication and the integration with all of the interested parties starts with the rollout. I think it needs to begin now as we continue to work through the questions.

Because I am sure there are people who are looking at it right now, because there's still a lot of work to do. I mean as part of the Committee, there's

more that has to be done to design the overarching rules for all of this, and I think it would be better to start including those who would have to digest all of this now, as opposed to as the -- we work all this out, and it will help us communicate it because I'm sure there are people who don't see this as just something other than a lab changing what we call stuff, and that's so far from what it is.

And so I would encourage us to begin to work with all the groups, those who were representatives, Org Reps, but others as well who are able to communicate this. There are a lot of national report cards that look at counting, and calling things, and helping people understand that as part of the process, so that all of that dissemination, discussion, understanding is built into the actual determination of what the final, sort of guidance is, and what the tables look like are going to be critical.

So, we choose words correctly, we choose

audiences correctly, and make sure everybody is at the table. That's actually where I think the heavier lift is, and I think that's why the Advisory Committee is so critical as part of this, is it's not just an APHL activity, but rather the Advisory Committee, and the diverse backgrounds of the members, as well as the Org Reps are going to need to make this massive change because what we're changing has been fundamental to the Advisory Committee's work over the last 20 years.

And so, if you're going to change it, then everybody who is part of the Committee action now, ought to be part of the formulation of the change, not just how do we describe what we decided to do to our partners.

DR. BERRY: This is the biggest change that's being suggested to the Recommended Uniform Screening Panel since we started having one, so is this going to be a process not an event? Oh yes. It is an opportunity to make things a lot better. I honestly

think so, but all of these comments about how do we make sure the people understand it and realize the promise that this brings is going to be critical to its utility.

So, I think all of us, and I'm sort of speaking words for everyone, but the people who spent all this time on this didn't spend this much time on these task force without the idea that we were trying to make things better, and that we have to make sure that's clear from this point on is what I think Scott is saying, if this is something that the Committee wants to entertain further, then we need to start right away.

DR. CALONGE: Great, thank you very much. Very great conversation, great presentation, and we do realize how much work went into what you presented in a short period of time. Thanks.

DR. BERRY: Thank you.

DR. CALONGE: Okay. So, my assumption is that we will debrief the information that occurred, we'll talk amongst staff, the Chair and the other

Committee Members, and we'll get back with you, thanks. I really appreciate it. Sorry, I'm missing something. Oh --

DR. DORLEY: No. We were wondering what the next steps were, and you just explained that, so thank you.

New Business

DR. CALONGE: Well, at this point I'd like to ask if there are any members with new business or announcements, and Melissa Parisi, I believe you would like to share a slide regarding a NIH research study.

DR. PARISI: Yes. Thank you. Can someone show, I think I just have two slides. This is just an announcement about the Rare Disease Clinical Research Network, which I think I mentioned at least verbally on our last meeting in May, but I had just wanted to remind folks here that this is an NIH initiative, that is really trying to involve as much research as possible on as many rare diseases as possible.

There are 11 out of the 27 institutes at the National Institutes of Health that are involved in this network, and really, they're trying to advance the diagnosis, management and treatment of rare diseases. And they focus on natural history studies as well as clinical trial readiness.

So, you know, some of the issues that arise for newborn screening conditions are a part of this network of consortia. The consortia -- currently there are 20 of them that are funded, and they have to at least have three rare diseases that are related in some way as part of their mission and their research focus.

And very importantly, they have to have partnerships with patient advocacy organizations. And so, this is a critical component of these consortia that is absolutely essential. They are supported by a data management coordinating center, and we are working very hard at NIH to ensure that all data generated are made publicly available, in a deidentified manner so that

they will be available to the larger community.

And currently the RDCRN is completing its fourth cycle. It has 20 consortiums studying 180 diseases across 273 clinical sites, both U.S. and international, and there are 127 affiliated patient advocacy groups. And the reason why this is relevant today is that the due date for the next cycle of competitions, those applications are due August 19th.

The program announcement is listed here. Obviously, if you haven't started your application, you're not going to be able to complete it in the next week and a half, but we are very excited by some of the queries that we've been receiving at NIH, and if you go to the second slide, especially around some of the topics related to newborn screening. Next slide.

And so, we are one of the 11 institutes and centers. NICHD is one of the 11 institutes and centers involved in the RDCRN, and our interests include newborn conditions, including those currently, or with the

potential to be added to the RUSP, and we are particularly interested in supporting natural history and longitudinal follow-up studies, and potentially even development of treatments for newborn-screenable conditions.

And then I've listed here other interests as part of NICHD, so we see this as kind of a follow-on to the Newborn Screening Translational Research Network which ended in the spring, and really is one of our efforts to promote research in rare diseases with an emphasis on newborn screening.

So, we'll keep you posted as, you know, the awards are made, it probably won't be until next summer, but just to let you all know that this is one of the activities that we're engaged in, trying to support research in newborn screening. Thank you.

DR. CALONGE: Thank, Melissa. Any other new business? Seeing none, I just want to remind everyone that next month, September is Sickle Cell and Newborn

Screening Month, so time to educate and raise awareness, and we appreciate the efforts of those in the room that support this.

I will remind you the next Advisory Committee Meeting will take place November 14th and 15th of this year. We plan to have the November meeting with virtual participation only. If there are any situational changes where we would have to shift our plans, we will make announcements on our website.

You could also find a full list of the meeting dates through 2025 on the website. And with that announcement, I would call the August Meeting of the Advisory Committee on Heritable Disorders in Newborns and Children adjourned. Thank you for all your participation, and thanks to all our staff, and IT folks, and other folks who support us logistically for a really great meeting.

I really appreciate it. Thanks.

(Whereupon the August Meeting of the Advisory

Committee on Heritable Disorders in Newborns and Children adjourned at 12:55 p.m.)