The Advisory Committee on

Heritable Disorders in Newborns and Children

U.S. Department of Health and Human Services

Virtual Meeting

Day 2

Friday, February 11, 2022

10:00 a.m.

Attended Via Webinar

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C O N T E N T S

P R O C E E D I N G S

WELCOME AND ROLL CALL

CYNTHIA POWELL: Good morning, everyone. Welcome to the send day of the February 2022 meeting of the Advisory Committee on Heritable Disorders in Newborns and Children.

I'm Dr. Cynthia Powell, Committee Chair. We will begin with taking the roll. For Committee members representing the Agency for Healthcare Research and Quality, Kamila Mistry.

KAMILA MISTRY: Here.

CYNTHIA POWELL: Kyle Brothers, Committee member.

KYLE BROTHERS: Here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: From the CDC, Carla Cuthbert.

CARLA CUTHBERT: I'm here.

CYNTHIA POWELL: From the FDA, Kellie Kelm.

KELLIE KELM: Here.

CYNTHIA POWELL: From Health Resources and Services Administration, Michael Warren.

MICHAEL WARREN: Here.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Here.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Here.

CYNTHIA POWELL: From the National Institutes of Health, Melissa Parisi.

MELISSA PARISI: Here.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Here.

CYNTHIA POWELL: And Cynthia Powell, I'm here. And Scott Shone.

SCOTT SHONE: Here.

CYNTHIA POWELL: Thank you. And now for our organizational representatives from the American Academy of Family Physicians, Robert Ostrander. I know you're here, Bob, I saw you before, so. I think he's here. He may be muted or --

American Academy of Pediatrics, Debra Freedenberg.

DEBRA FREEDENBERG: Here.

CYNTHIA POWELL: American College of Medical Genetics and Genomics, Maximilian Muenke.

MAXIMILIAN MUENKE: I'm here.

CYNTHIA POWELL: American College of Obstetricians and Gynecologist, Steven Ralston.

STEVEN RALSTON: I am here.

CYNTHIA POWELL: Association of Maternal and Child Health Programs, Sabra Anckner.

SABRA ANCKNER: Here.

CYNTHIA POWELL: Association of Public Health Laboratories, Susan Tanksley.

SUSAN TANKSLEY: I'm here.

CYNTHIA POWELL: Association of State and Territorial Health Officials. As mentioned yesterday, we do not have a representative yet, but hopefully we will have a new representative in the future. And Shakira Henderson from the Association of Women's Health Obstetric and Neonatal Nurses is unable to join us today.

There will not be a representative from the Child Neurology Society. From the Department of Defense, Jacob Hogue.

JACOB HOGUE: Here.

CYNTHIA POWELL: From Genetic Alliance, Natasha Bonhomme.

NATASHA BONHOMME: Here.

CYNTHIA POWELL: From the March of Dimes, Siobhan Dolan.

SIOBHAN DOLAN: Here.

CYNTHIA POWELL: From the National Society of Genetic Counselors, Cate Walsh Vockley.

CATE WALSH VOCKLEY: I'm here.

CYNTHIA POWELL: And from the Society of Inherited Metabolic Disorders, Gerard Berry.

GERARD BERRY: Here.

CYNTHIA POWELL: Thank you all.

KAMILA MISTRY: Dr. Powell, this is Kamila, I'm not sure if you could hear me or not, but I'm here.

CYNTHIA POWELL: I knew you were on, so thank you, Kamila. I know you were having some problems connecting, but glad to know that you're here.

KAMILA MISTRY: Thank you.

CYNTHIA POWELL: All right. So now I'm going to -- oh, go over the meeting topics for today. The first item on the agenda for today is the Phase 2 of update on the

evidence-based review for Guanidinoacetate methyltransferase or GAMT deficiency.

Next the Committee will have a discussion on its capacity to review multiple nominations per year. Today we'll have a second public comment period where we'll hear from Megan Pesch on the RUSP nomination of congenital cytomegalovirus; Heidi Wallis on the RUSP nomination of Guanidinoacetate methyltransferase deficiency; from Dylan Simon from the EveryLife Foundation for Rare Diseases; from Beth Vannoy from Minutes Matter MCADD, which is medium chain-CoA dehydrogenase deficiency; Mena Scavina from Parent Project Muscular Dystrophy.

After a break the Committee will receive a presentation on newborn screening and health equity. We plan to adjourn the meeting at 1:30 p.m. Eastern Time. And I'll now turn it over to Mia Morrison, our designated federal official.

MIA MORRISON: Thank you, Dr. Powell. Members of the public, audio will come through your computer speakers, so please make sure to have your computer speakers turned on. If you can't access the audio through your computer,

you may dial into the meeting using the telephone in the email with your Zoom link.

Committee members and organizational representatives, audio will come through your computer speakers as well and you will be able to speak using your computer microphone. If you can't access the audio or microphone through your computer, you may dial into the meeting using the telephone number in the email with your user specific Zoom link.

Please speak clearly and remember to state your name first to ensure proper recording for the Committee transcript and minutes. The Chair will call on Committee members and then organizational representatives. In order to better facilitate the discussion, Committee members and org reps should use the raise hand feature when you would like to make a comment or ask a question. Simply click on the participate icon and choose raise hand. Please note that depending on your device or operating system, the raise hand feature may be in a different location. And if you need to troubleshoot, please consult the webinar instruction page in your briefing book. Next slide, please.

To enable closed captioning, please select the closed captioning icon from your Zoom task bar. From that menu, select show subtitles.

And I'll turn it back over to Dr. Powell.

GUANIDINOACETATE METHYLTRANSFERASE (GAMT) DEFICIENCY EVIDENCE-BASED REVIEW – PHASE 2 UPDATE

CYNTHIA POWELL: Thank you, Mia.

In April of 2021 the Committee received a nomination for Guanidinoacetate methyltransferase deficiency for inclusion on the RUSP. This was the second time that GAMT had been nominated. At the August 2021 meeting the nomination and prioritization workgroup presented an overview of the nomination package and the Committee voted to move GAMT deficiency forward to full evidence-based review.

At the November 2021 meeting, the Committee received the Phase 1 update on the evidence-based review for GAMT deficiency. Today, Dr. Alex Kemper, lead for the evidence-based review group, and Dr. Lisa Prosser, ERG member, will provide the Committee with the Phase 2 update. And I'll turn things over to Alex.

ALEX KEMPER: Thank you very much, Dr. Powell. The purpose of the presentation today is just to provide a high-level insight into where we are with the GAMT deficiency review and point out what I think are some key findings as well as our plans moving forward.

I'm going to actually go ahead and do this whole presentation, including Dr. Prosser's part and you'll see why in a bit. Next slide, please.

First of all, this is our list of our ERG members. Again, I'd like to thank Dr. DeLuca and Dr. McCandless for serving as the liaisons for the Advisory Committee to our work. Next slide, please.

And this is a list of the technical expert panel members for this particular review. I've also marked those individuals who are also involved with the nomination of GAMT deficiency to be considered for the Recommended Uniform Screening Panel or the RUSP. I will say, as I have for the technical expert panel, we discussed yesterday for MPS II, the technical expert panel is really wonderful. It rallies provides great insight into the condition, sources of data and really how we consider emerging issues. So

again, I want to thank all members of the technical expert panel. Next slide, please.

So, I'm going to begin as I did last time with a brief overview of GAMT deficiency. Next slide, please.

So GAMT deficiency is a condition that causes cerebral creatine deficiency, and untreated that leads to global developmental delay with severe language delay, seizures, muscle weakness, movement disorders and significant behavior disorders. Next slide, please.

It's an autosomal recessive disease associated with mutation of the GAMT gene located on chromosome 19. You can see some details about that there. But the hallmark of the condition is elevated Guanidinoacetate or GUAC as I'll call it for the remainder of the presentation. And low plasma and brain creatine. Next slide, please.

This is a picture of the metabolic pathway. I'm going to revisit the metabolic pathway when I talk about treatments for GAMT deficiency, but again, I apologize because I don't have control over the arrow, but you can see where the GAMT enzyme is and how when it's there, it helps with the production of creatine, and when it's

absent, you have the buildup of guanidinoacetate. Next slide, please.

So, the pathophysiology of GAMT deficiency is related directly to the low creatine levels which lead to a significant and progressive intellectual disability when it's not treated. Interestingly, as I've read the studies about GAMT deficiency, it seems that the GUAC accumulation itself also leads to problems with the disorder including epilepsy and extrapyramidal disorders, the movement disorders that are associated with it.

In terms of evaluating the status of the condition, creatine and GUAC are the -- you know the standard blood measures that are followed. But interestingly, you can follow involvement with MR spectroscopy as well. There are a number of studies that use that to look at the involvement with the lack of creatine in the brain. Next slide, please.

In terms of the epidemiology, again, we've discussed this before, the estimated prevalence is under .2 cases per 100,000 live births. But in the studies that have been done of existing samples to estimate carrier frequency, there's really a fairly wide range in carrier

frequency. But again, it is a rare disorder. Next slide, please.

In terms of clinical identification, and as everyone knows, our job is really focused on comparing clinical identification to what might happen with newborn screening. When you look at clinical identification, there's really a wide range of when individuals are diagnosed with a condition. In fact, I have one study up here that showed a mean age of about 12 years with a range of 2 to 29, and I think some of this is due to the fact of misdiagnoses or under a diagnosis that, given the rarity, affected individuals might not ever get to the right diagnosis. As a matter of fact, I put up here a study that was a retrospective study that was done in France evaluating over 6,000 subjects with unexplained neurological symptoms and found seven cases. So, I think that speaks to the challenge of clinical identification and probably does add some uncertainty around what we know about the epidemiology of the condition. Next slide, please.

So, let's talk about newborn screening. Next slide, please. So, this slide provides an overview for the

screening and what's involved with diagnosis of GAMT deficiency in infancy. Diagnosis is based on tandem mass spec screening for GUAC, and creatine and the diagnosis are based on finding low creatine and elevated GUAC and plasma sometime after birth, like a week after birth.

There are other conditions that need to be ruled out, for example, arginase deficiency and other creatine disorder. And the molecular analysis is supportive. So again, just to highlight this again, screening is based on identifying GUAC and creatine in the dried blood spot and diagnosis is essentially measuring those things sometime a little bit after birth. Next slide, please.

So, I think I'll highlight some of the newborn screening activities in the United States. There are newborn screening activities outside of the United States, but for the purposes of the talk today I'm just focusing on the United States information. So, screening for GAMT deficiency began in New York in October 2018 using laboratory developed tests. It began with a two-tiered screening test, looking at GUAC and creatine, using a flow injected tandem mass spec. And then there was a second

tier GUAC by HPLC. But as it turns out, they didn't need that, the second tier was discontinued in September 2021.

As part of their evaluation, they do sequence the GAMT gene as part of the referral process. We talked about this before, that there are some newborn screening programs that include sequencing as part of their referral process, but again, that's not a critical thing for establishing the diagnosis, it's a biochemical diagnosis. But again, it can be helpful. Next slide, please.

So, in 2021 there were 211,242 newborns screened with seven borderline cases ultimately leading to six referrals, three per 100,000. And you can see the outcomes of those cases here, but there was one case that was identified in New York. Next slide, please.

In Utah, again, it's -- one of the things I want to remind the Advisory Committee as we talk about numbers of screens that were done, that Utah is a two-screen state. Each infant has two newborn screening. Screening for GAMT deficiency there began in June of 2015, again, using laboratory developed tests. From 2015 to 2019, they had a first-tier test based on GUAC and creatine using a derivatized assay and then second tier GUAG and creatine

re-test with liquid chromatography tandem mass spec. But now they use a non-derivatized method and again, the GUAC and creatine is done as a send-out, as listed here. Next slide, please.

So, since the adoption of the current approach in 2019 there were about 78,000 screens, again, two screen state, but there was one infant who was -- went on to get a second-tier test, and that infant went on as a referral and ultimately was a case that was identified. So, you can see the numbers per 100,000 screens here, not at the newborn level. Next slide, please.

So, I want to talk a little bit about treatment. Next slide. And I want to remind everyone of the metabolic pathway that's listed here, and the treatment as you might surmise by looking at where the anosmatic block is, is with ornithine supplements and creatine supplements. So, trying to, you know, minimize the buildup of GUAC, but you know, showing that there's ornithine for the urea cycle there and then replacing the creatine that is not being generated. Next slide, please.

So, the key thing about treatment, so it's creatine, ornithine and then sodium benzoate supplements.

These things are available over the counter. So, unlike some of the other conditions that we've talked about, the treatment is more readily available and certainly less expensive. In addition to the things, I talked about, there's dietary restriction of arginine. I should have mentioned that when we were looking at the diagram. You know, given the rarity of the disorder, the ideal timing of treatments is uncertain, but experts certainly recommend within a month of age. And then in addition to receiving the supplements there needs to be serum monitoring over time, and as the child ages, that can be -- the frequency can be reduced. But this, I hope, just gives you the flavor of what's involved with the treatment. Next slide, please.

So, what do we know about the effectiveness of early treatment? So, you will not be surprised that given the rarity of the condition, it's hard to do clinical trials and to conduct, you know, either a large prospective or retrospective cohort studies. So, I'm going to focus on some case reports and case series that I think gives insight into what we know about early treatment. Next slide, please.

So, the first one we're going to talk about is a case series of 48 subjects from 38 families that was collected through a survey of clinicians. You can see that for these subjects the median age of diagnosis was 51 months with a remarkable range of prenatal to 34 years where and treatment for all these subjects began soon after diagnosis.

Increasing age in treatment start was associated with greater severity of intellectual disability. So, this is no surprise, the longer that individuals went on without treatment the more likely that they're -- they're more likely to have intellectual disability. Three subjects who were treated before one month in this large case series with no developmental delay reported amongst those three subjects after, you know, a fairly variable period of treatment, ranging from 14 months to seven years. So again, this gives you some insight into the potential benefit of early treatment. Next slide, please.

Another case report that we identified described the subject who began treatment at 28 months, who is followed to six years with persistent intellectual disabilities. So, I put this case report out try to figure

out like where, you know, where is it that treatment really needs to begin to make a difference? And I don't want to contrast that with another case report of a subject who was diagnosed and treated at eight days of life. This individual was diagnosed based upon family history, and at least as far as 12 months, which is what's been reported, that individual had normal development. Next slide, please.

I'm going to talk about some sibling cases. Here's a case report of an older sibling who was treated at 10 months after presenting with hypotonia, and at six years still had delayed speech and fine motor skills. Again, I'm not able to go into greater detail about the developmental status of the individual, I just can go with what's been reported.

But I'm going to contrast that with the younger sibling who was diagnosed prenatally and is normal at 42 months. Next slide, please.

Here's another example. It's an older sibling who was diagnosed at two years of age after presenting with significant developmental delay and seizures, and that sibling -- that individual's younger sibling began

treatment at 22 days and is reported to be developmentally mobile at 14 months. Next slide, please.

And here's an abstract that we identified reporting cousins. So, an older cousin began treatment around three years of age and it was unclear in the abstract how long the subject had been treated, but this individual did have significant intellectual impairment, but did seem to have improved seizure frequency. In contrast, the younger cousin, who was evaluated at five months had normal development at 16 months. Again, you know, there's limited information in abstracts. Next slide, please.

Actually, can you go back one slide, because I just want to finish this part up before I make a little bit of a transition. Given the rarity of GAMT deficiency, it's going to be these kinds of case studies and sibling studies that are going to provide the best evidence regarding the benefit of early intervention versus clinical case identification. In many ways this is similar to the information that we described yesterday. Next slide, please.

So, our evidence review is from a screening standpoint, we're continuing to gather screening information, both, you know, within the United States and elsewhere, as I described before, and on the treatment side, really focusing on what we can find comparing early identification to later identification. Next slide, please.

So, you know, this brings up the issue of the projection population level outcomes. Next slide, please.

And as with yesterday, the goal of that is to compare projected outcomes from GAMT deficiency newborn screening for all newborns born in the United States, the 3.6 million infants born each year, with usual case detection in the absence of screening. Next slide, please.

And you know, this modeling, again, is going to be very similar to what we showed yesterday in terms of screening outcomes, the number of cases with GAMT deficiency that might be identified and compare that to the number that would be expected through clinical identification. Next slide, please.

And this is the model showing a hypothetical cohort of newborns in the United States who either have

newborn screening or go through the process of usual clinical identification, and we can report positive screens, negative screens, and false positives then risk confirmed GAMT deficiency. And all these short-term outcomes related to GAMT deficiency, but the level of evidence, I do not believe is going to be sufficient to be able to model longer term outcomes of newborn screening simply because of the -- you know, the rarity of the condition and the needs are focused really on these cases series and sibling studies. So, in many ways it's a similar story to yesterday. Next slide, please.

In terms of the public health system impact survey -- next slide, please -- and as you know, that's to assess the readiness and feasibility of newborn screening programs to implement screening for GAMT deficiency. APHL, through the work of Jelili Ojodu and Elizabeth Jones, coordinated a webinar that was held on January 14th, and the survey is to open next week, and APHL will be pushing all sorts of reminders and pushing people, haranguing people to make sure that those surveys are filled out -- are completed. And of course, APHL will also be conducting in person interviews with the programs that have adopted

newborn screening for GAMT deficiency as well as some others that might be representative of those who are not screening. So, all that work is moving ahead as we normally would Next slide, please.

So, I'd like to just stop there and see if there are any questions about either where we are with GAMT deficiency or if there are recommendations for anything that you'd like us to look at in particular.

CYNTHIA POWELL: Thank you, Dr. Kemper. Yes, we will now open it up for questions, first from Committee members and then from organizational representatives, understanding that this is a high-level discussion at this point as Dr. Kemper and the ERG will complete their work over the next three months and the Committee will see their final report prior to our next meeting, and we'll hear from our Committee representatives on the ERG and their recommendation at that time.

So as usual, remember to use the raise hand feature and state your first and last names for the record. Jennifer Kwon.

JENNIFER KWON: Hi, it's Jennifer Kwon. Alex, you had said that New York, they were doing sequencing as part

of their newborn screening process, I think that's what I heard. So, I was just a little -- I was interested in what to make of the five false positives.

ALEX KEMPER: I had to actually pull up the numbers again to take a look at it. What I can tell you, again, is that, you know, screening, the sequencing is baked into the -- into the process. In terms of the details of, you know, why exactly those false positives happen and those kinds of things, I can come back to you with that later.

JENNIFER KWON: Yeah, I think that would be helpful just for the -- I mean, I know that this is still ongoing, but I think that that would be helpful to know, because the New York State Lab has a -- I mean, I think clinicians are really comfortable with the amount of information they get from the New York State Lab because it really helps with clinical decision making. I was just curious about what maybe the variants were of uncertain significance and you now, some of those details, I think, will be helpful for the Committee --

ALEX KEMPER: What's really interesting is, you know, when we're talking to the technical expert panel, I

mean, it's clear that it's really -- it's a biochemical diagnosis, so figuring out exactly what the role is, but we can clarify that more for you. As a matter of fact, I can send a follow-up email to the Committee if you want to find out before three months from now.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Thank you, Shawn McCandless, Committee member. Thanks for that update, Alex. Just a few questions for clarification, some of which you may be able to clarify now and some of which would be for the future. The first is that one of the slides said that in Utah they use something called FIA mass spec, mass spec. I assume that that's flow injection analysis.

ALEX KEMPER: Yes.

SHAWN MCCANDLESS: And just to confirm, that's pretty much the standard for tandem mass spectrometry, correct?

ALEX KEMPER: Yeah.

SHAWN MCCANDLESS: Great. Okay, so that's -- this is nothing special, it's just --

ALEX KEMPER: No, it's nothing special as opposed to like the HPLC and the LC stuff that I've been talking about before.

SHAWN MCCANDLESS: Yeah. Yeah, good. So pretty much every state lab would already have this equipment to do this? So, the assay might be different, might require some additional steps, but the equipment --

ALEX KEMPER: Well, what I can tell you is both the New York and the Utah screeners, as well as, you know, we spoke to experts in Canada that are involved in newborn screening for it as well that you know, they'd like to highlight that this is, you know, as close to something that's easy to add into existing tandem mass spec screening, as you can hope. Now, I don't want to like cross lines and see them, you know, pushing forward or not, but from their perspective, it's really just a marginal amount of additional work.

SHAWN MCCANDLESS: Great, thank you. The second thing is that you made the statement that all of the treatment, sodium benzoate, creatine and ornithine are available over the counter. Almost certainly at least the creatine and ornithine will be considered nutritional

supplements by insurance companies and not covered, so it would be really helpful to have estimates of the expected cost of treatment for families, since there's -- unless there's some requirement that these treatments be covered. If this as added to newborn screening this is almost certainly going to create -- create a requirement for the family to pay for the treatment themselves, and we would -- I think it would be helpful to know what that burden would be.

ALEX KEMPER: So, there's kind of two things related to that that I want to look at. One is, you know, the issue of cost and coverage like you talked about, and the other thing is that if families opt to, you know, just buy it over the counter, go to Amazon or wherever it is that you can get this, are the standards such that they can feel reassured that they're getting the good stuff. And that's something that we'll have to rely on the technical expert panel to help us understand, but obviously if they're getting it over the counter, we want to make sure that they're getting the highest quality product.

SHAWN MCCANDLESS: Right. Yeah, that's a great point. The final point that I would make is particularly

pertinent, I think, after yesterday's evidence review and discussion, and that is that we have time right now to go back to the nominators and ask them -- there are very few case reports, as you alluded to. There's plenty of time for somebody to go back and track down every one of those reporters and compile a new list of updated information on long term outcomes. And that would -- and if any of you are listening, any of the people on the nominating Committee, this would be very, very helpful in making a decision if we had that kind of updated data and if it can be put together in time that it could be peer reviewed, of we review it, that would be even better. I'll stop there.

ALEX KEMPER: Yeah. No, I'm glad you made that recommendation.

CYNTHIA POWELL: Yeah, thanks for bringing up, too, about the cost of supplements and you know, thinking of biotinides deficiency and Biotene over the counter and you know, for some families it's nothing, it's minor, you know, added expense, but for some -- for other families it can be quite a burden. So, I think that will be important for us to hear more about. Scott Shone.

SCOTT SHONE: Thanks. So I think, Alex, for following up on what Dr. McCandless was saying, around the flow-injection mass spec, I think it would be good in the presentation in a few months to dive into a little bit more on how that's added to the existing amino acid ascertained and lysosomal storage disorder screening, the first tier, and a little bit on what's going to -- because there's no FDA cleared assay, so how does that going to be a burden? Probably going to come up in the public health system's impact assessment survey, so I would ask Jelili to really ask some of those questions, particularly the New York Lab, I think, runs an LDT, but Utah is running an FDA cleared kit. So, it would be good to understand that a little bit more and just what that burden would be. Like it is likely easy to add just to get the regulatory burden on the labs to do that.

And I also wondered if you know now or maybe in the future, why was this second-tier assay discontinued in New York and then transitioned to a send-out in Utah? My guess is that because of the low number of babies being reflexed, it was too burdensome to maintain, but is that accurate?

ALEX KEMPER: Yeah, no, that's accurate. And then the New York, I actually have detailed information but not at my hands, but basically, they felt that they could get away with just going directly without the second tier, and to use their vernacular, the juice wasn't worth the squeeze that they were, you know, finding what they wanted to find. But again, you know, that's the kind of thing that when we come back in three months, we'll go through in deeper detail.

CYNTHIA POWELL: Any other questions or -- Shawn McCandless, did you have --

SHAWN MCCANDLESS: Yeah, just Alex, I'm wondering if when we get a more detailed report whether there will be information from the other newborn screening programs you alluded to outside of the U.S.?

ALEX KEMPER: Yes.

SHAWN MCCANDLESS: Okay, great. Thanks.

CYNTHIA POWELL: And now we can open it up to organizational representatives. Gerry Berry.

GERARD BERRY: So, hi, Alex, this is Gerry. I want to be careful of what I say about his because I've not studied it properly, but there is some difference in the

flux that exists in the utilization of arginine through the normal pathway that involved aerogenesis versus the pathway where there's entry into the mitochondria for biosynthesis and this sometimes causes some problems in the newborn period with regard to being able to make diagnoses with some other disease processes, and I think it's something that we ought to study a little more. There may be a problem where some infants might not be detected whereas others would because of this shift and flux that exists in the newborn period.

ALEX KEMPER: I think I know what you mean, but it's -- well, I'm a general pediatrician, so I always get feverous when I look at the Krebs cycle again. So, what I will do is follow up with you afterwards just to make sure that I understand the specific question, because I want to make sure that I get it answered appropriately.

GERARD BERRY: Yes. Yes, I think we should look at this a little more carefully. There is another disorder where the flux is completely different in the newborn period and so you're not able to make a diagnosis, and I wonder whether that might have an impact on false -- you know, on the false negatives.

ALEX KEMPER: Yeah, I have no idea, but we will investigate.

GERARD BERRY: Yeah. It could be trivial, but it deserves some investigation. Thank you.

CYNTHIA POWELL: Any other comments or questions for Dr. Kemper? Yes, Chanika.

CHANIKA PHORNPHUTKUL: Dr. Kemper, will this newborn screening technology pick up other types of creatine deficiencies as a secondary finding because of the X-Linked transporter which would probably be more common or are they just going to use GUAC as their primary and then secondary to the creatine?

ALEX KEMPER: Correct. So, I don't think it's going to pick up the -- again, I can confirm that with our technical expert panel as well, but really, the focus is on GAMT deficiency and measuring GUAC and then looking at the GUAC and the creatine ratio.

CYNTHIA POWELL: Any other questions? All right, well, thank you very much, Dr. Kemper and to your team, and we look forward to discussion at our next meeting.

ALEX KEMPER: All right, thank you very much.

ACHDNC CONDITION REVIEW CAPACITY- INITIAL DISCUSSION

CYNTHIA POWELL: All right, going on now, we're going to talk about the Committee's condition review capacity and initial discussion about this. As technology for newborn screening and treatment of rare heritable disorders advances, there's an increasing possibility that the number of condition nominations will outpace the Committee's capacity to review nomination packages and conduct evidence-based reviews.

The Committee has heard from multiple stakeholders about this potential scenario. In August of 2021 the Committee began exploring issues concerning this scenario in a presentation and discussion facilitated by Dr. Shawn McCandless. During this discussion the Committee discussed the timeline and approach for conducting evidence-based reviews. Committee capacity and issues concerning the equity of the nomination process were also discussed. Next slide, please.

The Committee is budgeted to conduct two evidence-based reviews per year and must also balance Committee member capacity and the rigor of reviewing nomination packages. Even with a larger Committee budget

and/or scaled up approach to conducting evidence-based reviews, most states would not be able to keep pace with implementing multiple newborn screening conditions added to the Recommended Uniform Screening Panel in a short time frame. It currently takes most states between three to ten years to implement a new RUSP condition. The expertise of the Committee and the evidence review group is critical. The Secretary recommends that every state screen for conditions on the RUSP because the ACHDNC has rigorous methods in place to assess complicated data and undertake an informed decision-making process.

It might not be feasible to make condition reviews less intensive or to scale up and conduct the same level of review and analysis. The nomination and prioritization workgroup has well defined criteria in place to review nomination packages, however, I've identified it as priority to define criteria for the prioritization of nominated conditions.

On the next slide I'll pose a few questions for your consideration, but before I do, please keep in mind that the Committee and the N&P workgroup have a finite capacity to review nomination packages. Next slide.

I feel that a key strategy will be to develop criteria to prioritize the review of nomination packages. To that end and in building on today's discussion, within the next few weeks I will convene a workgroup comprised of both current and former members of the Advisory Committee and other newborn screening and subject matter experts to discuss these issues.

Today it's important to gather your initial thoughts on this topic. For example. What are your thoughts on criteria for prioritization? What are the characteristics of a nomination package or condition that should be prioritized? What are your ideas for this process? From a different perspective, are there certain factors that would make a nomination package or condition not ideal for prioritization? What would the process look like? For example, would the entire Committee vote to prioritize or not prioritize the condition. In the event that the Committee receives multiple nominations at one time, should there be more than one N&P workgroup?

I will now open up the floor for discussion. Committee members will discuss first, and organizational representatives will follow. As a reminder, please use the

raised hand feature in Zoom when you'd like to make comments or ask questions. When speaking, please remember to unmute yourself and state your first and last name each time you ask a question or provide comments to ensure proper recording.

I'll say there was a paper that was published in December, a project done by Don Bailey, Holly Peay and others at RTI International that surveyed newborn screening stakeholders and got some of their thoughts about this issue and others just related to the advancement of treatment for rare diseases and how this Committee and newborn screening programs in general will be able to handle this. So, you might want to take a look at that if you haven't seen it already. Jennifer Kwon.

JENNIFER KWON: Hi, this is Jennifer Kwon, and I can't believe -- I know, it looks like I'm a megalomaniac because I'm always the first one talking, but I think this is an incredibly important issue, and I care a lot about newborn screening, and I think that our ability to sustain high quality newborn screening follow-up is really going to be impacted by the number of -- the number of conditions and people who are applicants for those conditions, who are

going to have new treatments that are being developed right now. I mean, I just feel like this is sort of coming down the pike.

So as a new member, I have to say I'm not that familiar with the nomination and prioritization workgroup that you were discussing. I was wondering if you could share a little more about how they get formed and you know, how they're sort of brought online, Dr. Powell, if you wouldn't mind doing that?

CYNTHIA POWELL: Sure. Sure. So, the N&P workgroup is made up of four Committee members plus the Chair of the Committee and we try to get, you know, a fairly wide range of expertise in that area, you know. So, for clinician, newborn screening lab expert, someone with more primary care background, as well as knowledge and interest and expertise and ethical issues. And also, we have a representative from the -- currently from the CDC, Carla Cuthbert serves on that workgroup.

JENNIFER KWON: So, you choose them as soon as you see an application come in, basically?

CYNTHIA POWELL: No, it's a standing -- pretty much been a standing workgroup. So that, you know, unless

people rotate off the Committee, they, you know, continue to serve possibly indefinitely, but yeah, so --

JENNIFER KWON: If they look at the -- they're the first people to look at the application?

CYNTHIA POWELL: Yeah, so well HRSA -- so the application is submitted to HRSA and HRSA reviews the application. And then if, you know, there are things that are missing, you know, they will go back to the nominators and ask for that additional information. And you know, getting that back could take just, you know, a few weeks. It could take months, and then after package is complete as per HRSA, then it's given to the N&P workgroup for their review. And then usually it takes at least three meetings of the N&P workgroup to discuss the package, to go over all the questions that the N&P workgroup needs to answer prior to submitting there, you know, review to the full Committee, and going over those questions and you know, guidance, whether, you know, it's thought that the package is ready for -- or nomination is ready for a full evidence based review or not.

JENNIFER KWON: Thank you.

CYNTHIA POWELL: Sure. Kyle Brothers.

KYLE BROTHERS: Thank you. I think I'm contractually obligated to mention ethical issues when topics like this come up, so I'll just do that. So, in other domains of health, you know, prioritization is based by an analogy on military triage, right? We focus our resources on the patients that can be helped the most, and fortunately, this has come up during COVID with prioritization of ICU beds and ventilators and things like that.

Unfortunately, I think in this case that framework might not work so well, because we're deciding whether to do an evidence review, and it's really the evidence review that could help us assess what's our capability of helping, you know, children, you know, by proceeding with this process. So I think it might be difficult from the beginning to say, you know, this condition, because it is a more common condition, or because we think the intervention is more beneficial that it should have a priority, so I think I could be convinced otherwise, but I think criteria like that might be difficult to implement in a state of sort of like initial, you now, lack of information. We have some, you know,

projections about what the evidence says, but we don't really know until we get a full review.

So maybe -- I think there are a few possible solutions to that. One would be to say we can only consider and vote on conditions and prioritize that after a review. So it might be that we need to scale up our ability to do an evidence review while still accepting that we can only view one condition per meeting or something like that, in which case I think we would need to change the guidelines for the Committee, because we have a specification about how much time passes between a nomination and a vote for further consideration.

But another approach might be to simply take a first come, first serve framework, and say there's no meaningful way to prioritize conditions because there are many, you know, value judgments involved in that. So, we will say from the date that a nomination is fully, you know, completed, it goes in the cue, and we will reach it as soon as we work through all the ones before that one in the cue.

So anyway, just some ideas on how we might approach this.

CYNTHIA POWELL: Thank you. Yeah, there has been discussion about whether the N&P workgroup should do more detailed review prior to sort of, you know, making their recommendation. And you know, that's certainly an option. One of the difficulties in that is, you know, they're Committee members, they're already doing this as, you know, volunteer work, dedicating their time to this, and to really carry out a thorough evidence-based review, you know, is, I think, going to be difficult. We're currently short on a couple of Committee members. You know, that happened when, you know the Newborn Screening Saves Lives Act was not passed and we're still operating as a discretionary Committee. We're hoping to add some new members, you know, within the next year. But, you know, it has been difficult to sort of, you know, just have the time to review everything. So anyway, but thanks for your comments, Kyle. Scott Shone.

SCOTT SHONE: Thank you. I have a couple of different and desperate thoughts on this, and I'll try to articulate clearly. So, I would just say as a member of the N&P workgroup I agree with everything Dr. Powell said. I mean, there are -- and we've had it recently with this

one after the other of MPS II and GAMT, and CCMV and more that I'm --

CYNTHIA POWELL: Krabbe.

SCOTT SHONE: Krabbe, thank you. And Krabbe, and I just want to acknowledge the work of my colleagues on the N&P workgroup to really be diligent about that. And I think, Kyle, your point around not making value judgments is something that we have really taken to heart. We're not doing that, right? We're not trying to do an evidence-based review, but the reality is that the product that comes in drives the amount of effort and the pace at which they can be assessed and pushed through, and we've seen that with some conditions that have come through in my tenure on the N&P workgroup can get done in a couple meetings and some have taken a few months of back and forth and reschedule and multiple meeting in a week or over weeks because everybody is trying to do their best to get it through.

So, I think the education efforts of HRSA to help nominators home in on what's critical in the nomination package is essential to make the work of the N&P group easier. That then just unfortunately shifts the bottleneck

to the ERG, and really thinking about do there need to be multiple ERGs. Alex Kemper is superman, but I think that even his cape only extends so far, and so -- and so I feel that we need to evaluate not only the N&P process, but also the ERG, and as Dr. Powell articulated, there's only currently budgeting for two a year, which inherently restricts the number that can go through.

But I do fear the tsunami that many people have talked about for a while. Don Bailey, when he was a member of this Committee talked about it and he's still publishing about it. So, I think that's very critical.

I want to say that, you know, I picked up on Dr. Powell, in your introduction. You said that numerous state programs are taking between three and ten years to implement disorders after addition to the RUSP, and I'm sorry to be a broken record, but as Bob said, Bob Ostrander said yesterday, this is what he and I do, is that even yesterday we talked about one to three. So, it's taking programs a while, depending upon the condition, to get these going. So, we have multiple funnels and I worry that we're going to get back to the situation we were in before this Committee started, which is then individual states are

going to get ahead of sort of national recommendations. And so, I think we have to get this done, and we're already getting to that position. So, my suggestion, I guess, would be that the criteria for submission to the N&P workgroup and what we do at the N&P workgroup can be evaluated and make sure that we're still, you know, in agreement that that's -- that is what should hold. Maybe there is more that we could do at the N&P workgroup to help facilitate the ERG, but it still doesn't get to what if three came in on the same day and how do we do that. And I don't have a good answer for that, and I'm hoping that the group that you pulled together can dive into what are the options for that.

CYNTHIA POWELL: Thank you. Chanika.

CHANIKA PHORNPHUTKUL: I'm Chanika Phornphutkul, a Committee member. I completely agree and I think -- I appreciate Kyle saying that you know -- we can't really use the incidents or the treatment as the drivers. I think considering, you know, first come, first serve seems practical, but I also think that maybe that's an opportunity to -- and I recognize the challenges of the resources to address and review and all that. So perhaps

if we built in that if there are a backlog, is there an opportunity to expand the Committee or increase the resources that go to this rather than this being a quote unquote volunteer, but it's a really more of a job from, you know, whatever federal government branch that really has to take this into account as part of caring for children. But I think it's probably a lot more complicated than what I'm trying to say. Thanks.

CYNTHIA POWELL: No, that's important. Thanks for that feedback. Jennifer Kwon.

JENNIFER KWON: Hi, it's Jennifer Kwon. Well, Scott, I was really hoping that you would share some changes for what should be prioritized, and I think that what I might say at this point, maybe in answer to what Kyle had brought up is that I do want -- I mean, I think we all want to be fair. We all recognize that maybe taking it first come, first serve might inadvertently reward those who have better resources for a variety of reasons. And so, I think we do want to have criteria.

I think this is a great opportunity because Dr. Powell has pointed out, we are a little bit in a crisis. I think that there are reasons why states are having a hard

time putting conditions on their panel that we recommended. I think that it's starting to feel a little less uniform across the country and I think that if we can show that we're being thoughtful in these difficult times about what we look at and what we sort of push forward for more evidence, that may be helpful.

I just -- you know, I was struggling thinking, oh, you know, an obvious priority would be if this is a condition where the majority of those found to be affected clearly had early treatment. And by early treatment, I mean treatment that starts in infancy. That is a condition -- I mean, that would seem like an obvious, you know, like condition to move forward, but we all know how even that type of criteria has so many problems. So, I think establishing another workgroup to take a look at this is a great idea. Thanks.

CYNTHIA POWELL: Thank you. Shawn McCandless. And I will get to the organizational representatives, I just need to call on the Committee members first, I'm sorry.

SHAWN MCCANDLESS: Thank you. This is Shawn McCandless, Committee member. I'll try to be brief because

I think Jennifer said much of what I was going to say. I just want to push -- I just want to say though, I think that we have an obligation to not use a first come, first serve approach. I think we have to -- we have to be able to prioritize, and I don't think we have to reinvent the wheel, I think there are very clear criteria that have been proposed over many, many years for how to assess newborn screening. You know, what is appropriate for newborn screening?

And I think that having some -- trying -- having a workgroup that's going to work on trying to objectify as much as possible a measurement of impact of a screening program that's being nominated up front so that the person nominating, or the group nominating comes in with data, as much is as known about prevalence, about the effectiveness of therapy, about the need for -- or the benefit of initiating therapy prior to the onset of symptoms, the quality of long term outcome data, and the feasibility of screening. We could create an objective measure that would allow for -- it's not going to be completely objective, but it would be a fairly objective prioritization program that we could use to say this particular nomination up

front appears to have significantly higher impact on the population based compulsory newborn screening program than another nomination.

So, I'm strongly opposed to us settling for a first in, first out. I think that has many problems with equity and with appropriateness. And I think that we can look at impact because it's not a big secret of what an impactful newborn screening program should look like.

The second is that I think we should up front ask the nominator to make the argument for why newborn screening is the appropriate way for screening for this condition, because I don't think that, as Chanika said, and others have said, newborn screening is not the solution to every -- the treatment of every condition in childhood. There are thousands of genetic disorders in childhood, and we will crush the system if we add all of them to the newborn screening program. So we have to be really thoughtful about what's realistic and we need to incorporate that into the prioritization process, and I think one way to start doing that is to insist that the nominating Committee have considered other options for screening, whether it's carrier screening whether there's

population based screening postnatally that we always shy away from, but it's the standard of care in other aspects of our healthcare system, and it's done in discussion with the families. So, I really don't understand why we are not able to discuss that around childhood diseases.

And so, I think there's many issues we could take into account, and I really appreciate your thoughtfulness about this, Dr. Powell, in creating a task force or a workgroup to look at it and make recommendations to HRSA and HHS about how we might move forward in a more effective way. Thank you.

CYNTHIA POWELL: Thank you. Natasha Bonhomme.

NATASHA BONHOMME: Hello, Natasha Bonhomme, Genetic Alliance. Thank you for the opportunity to have this discussion. I'm finding myself in a bit of a funny place because I don't think I typically disagree with Dr. McCandless, but I have to say that I, too, think that we really have to look at the equity issues around this, and I don't know how you avoid that by not going in a cue. So, I strongly want to make sure that that remains on the table to discuss, because I don't want there to be the assumption that every condition that we would be looking at has the

same resources behind it. And so, if you're going to base it off of an application, an application that looks good and has all the data and you know, is exactly what makes it easier to go through, maybe has support, or I shouldn't say maybe. It most likely has a level of support and funding that another group may not, another condition group may not have. I think this is particularly the case that, you know not all advocacy groups are structured the same way. Not all advocacy groups who oftentimes may be behind the scenes pulling together the materials, pulling together, providing, often, voluntary support to researchers and clinicians to get these applications together. They don't all have the same type of support. They may not have the industry ties that other groups do.

And I think to start to prioritize -- again, I think this is why we need a separate group to really parse out these issues, but it is not all created equal, and I would hate for a family to think just because their advocacy groups and their community is less resourced, and I mean not both money, but also time and a lot of other things that go into this is because they are always, you

know, third in line, and third in line again and again. So, I think that really needs to be looked at.

My other point is I think no matter what happens in this, we have to be really clear in terms of what is the purpose of this Committee and what is the expectation that is being set? Are we setting an expectation that this Committee meets the pace of treatments that are available? I don't have a yes or a no to that, but that is really telling, right? That then would inform okay, do you actually need five N&P Committees now?

So just -- I think that's going to be an important piece too, just what is the expectation both explicitly and implicitly that you're setting around this. But I'm really happy that we're truly diving into this conversation now and appreciate the opportunity. Thank you.

CYNTHIA POWELL: Thank you. Sabra Anckner.

SABRA ANCKNER: Hi, Sabra Anckner from AMCHP. Again, I want to echo Natasha. I'm glad that we're talking about this. I also want to say, and you know, Dr. Powell and Dr. Shone touched on this a little bit, but if it's bad for y'all how bad is it for the states, and for the

programs? You know, they don't get funding for two conditions a year. They get funding for no conditions a year. And they don't get to leave behind the one -- you know, you guys are done with MPS II now. The jurisdictions at the programs are not. And so, I just really, really want to emphasize that. If this -- you know, if this has a small subset of the work to do, is daunted by the amount of work there is to really reflect on what this pace does to the programs that are operating and their ability to do it well.

I want to just -- maybe this is almost too simple of a thought, but instead of having a rolling deadline, consider having specific like say maybe there are two times a year that there is a deadline for applications beyond just the equity issues that I agree a first come, first serve approach creates.

There's also the race that it can create, and the, I want to get my package in now even though I know there's a new paper coming out next week. But I'm not going to wait for it because I want to edge out whatever other potential nomination, I think there is. That would also ease whatever kind of prioritization or choice making

is needed to happen can happen all at once, because I also think like how you do prioritization when things are trickling in. Like oh, well now we were doing this one but now these guys jump over and we're going to leave this mid-stream. It just doesn't seem realistic. So, I would just really encourage thinking about deadlines like as a place to start.

And you know, to Dr. McCandless's point about is newborn screening the best way for things to be detected? The other thing I wanted to throw out there is, I feel like we're hearing somewhat newborn screening as a solution to diagnostic odyssey, and it is -- can't be that solution, because as we've seen with MPS II, it can create new diagnostic odysseys, so it's not just a case of whether prenatal screen -- you know, prenatal screening, or carrier screening or screening in childhood is the option but also better education of providers and linkages, and again, systems of care so that, you know, primary care providers are seeing something they're not sure of that they have places to go more quickly so that families aren't journeying for several years.

And then the last thing that I want to say is, you know, and these are things I couldn't say when I was managing a program, and I think that that comes up a lot when -- and things we talked about yesterday and in the reports that some of the lack of adoption that you're seeing is capacity, and some of it is a choice that they're not convinced, the programs aren't convinced that -- which did not used to be the case. It used to be that if something was on the RUSP, everybody was, you know, ready to go. And so, I think that that's something for the Committee to consider, there are some disorders that are simply not getting picked up by the majority of places where there is not a legislative mandate to do so, and it is -- I think they're feet, you know, APHL survey does not ask, do you want to screen for this disorder? If recommended in the past, if it included that question, I don't know how many people would be able to say no, because of the political implications there, but that's a factor that is not being discussed here that I think is really important.

And so yeah, I just really -- whenever this Committee is having a challenge, the labs and follow up

programs and sub-specialists that are our consultants, et cetera, are having them tenfold, and I really just want to center that.

CYNTHIA POWELL: Thank you. Steven Ralston.

STEVEN RALSTON: Thanks so much. I'm here for the American College of OB/GYN. I am a maternal fetal medicine specialist and I've been an ethicist for most of my career as well, and so I just -- I don't have very much substantive to add to this conversation, I just wanted to thank you for reminding me of some of these rare metabolic pathways that I haven't had to think about for 30 some odd years, but I cannot emphasize how important it is for us to continue to think about these equity and justice issues as we are thinking about the very scarce resources that we have in our genetics professionals. And I think about this from the perspective of OB because we are running into the same issues now with prenatal screening, and carrier screening, and having all of the counselors and geneticists that we need available to counsel about the many, many, many diseases we are screening for now. And as many of you know, ACMG just came out with their new recommendations for

carrier screening, which is going to set an even larger burden on the very scarce resources that we have.

And you know, it may be that newborn screening is going to become moot because it's all going to be pre-newborn screening eventually and that we're going to have whole Exome sequencing from a fetal stick of a pregnant woman in the future, but I have grave concerns about the capacity of the system to deal with all this. And when we are counseling our pregnant patients about newborn screening, because that's who does it, initially, is the obstetrician, and we're telling them that it's very unusual that you're going to get a positive result, but the more diseases that we screen for, the more false positives we're going to get, and this is going to be burdensome on both the professionals that are dealing with it and on the patients, themselves. Thanks.

CYNTHIA POWELL: Thank you. Scott Shone.

SCOTT SHONE: Thank you, Dr. Powell, and thank you, Dr. Ralston, for your comments, and I love that ACOG is represented and part of the whole discussion on education, I really appreciate the comment you just made about the role of OBs in newborn screening.

So going back to what Sabra Anckner said, you know, I do want to just say it's important to articulate that -- I don't think she meant it this way, but she said programs might be choosing not to. And I don't think it's programs. Let me be clear. Programs are not choosing to not -- let me back up, I don't want to do a double negative. Programs are not making the choice of whether or not to add a condition. It is the system in which they are placed in their individual state that has conditions conducive to more rapid implementation or slower implementation. Dr. Tanksley has my favorite figure of all time, the jellybean diagram system of newborn screening. And what I think needs to be added to that is procurement and HR, and facility management, and construction, and all of those precede the one to three years that I keep joking about, right?

And I don't mean to make about it, but one to three years assumes you're already. And that's true. Like I actually agree. Once the construction is done and the procurement, the contracts in place and people are hired, it actually probably takes two years for most programs, if not less. But there are years in advance, so programs are

working on all of this. I don't think anybody should take away the message that programs are making a choice not to do this. Every newborn screener in this country is dedicated to the health, safety, and well-being of newborns when they come into their state. And so that is a constant effort.

And I think that what I'm worried about is there is a growing number of requirement legislation spreading. We have now in North Carolina that you have to implement within three years of RUSP. That's -- that makes our RUSP more of a required universal screening pattern than a recommended, and I think that's a burden we now need to understand and bear, and when we do this, we need to understand that there is that system of not only the newborn screening program, but the physicians and clinicians and everybody else that's involved in the insurance and the Medicaid that has to catch up.

So, requiring a newborn screening program to add something is short sided when it's the newborn screening system and the healthcare system that has to take on the burden. And I thought about this as others are talking, and I would like to call my other federal partners to talk

about this. This is a -- I mean, it's HRSA sub-Committee, but we're advisory to the Secretary of HHS under this HRSA and NIH and CDC and other agencies fall, and I'd really like to suggest, Dr. Powell, that in the task force you bring together, that we identify ways for those agencies to have cross functionality. And maybe it's already going on and I'm ignorant to it. And what I would love to hear is at the next meeting, what's going on to link the pilot studies that Dr. Parisi's team is looking for and identifying and moving forward with, and the method development and the quality control method development that Dr. Cuthbert's team is so desperately working on, and the long-term follow-up and the education campaign and how are they linked? Because if we can link them all together, we might have better success on all of the things we've been talking about. Thank you.

CYNTHIA POWELL: Thank you. Debra Freedenberg.

DEBRA FREEDENBERG: Debra Freedenberg. So, there are a couple of things that I just wanted to comment on. One is very specific and when we think about when moving screening out of newborn screening, the equity issue becomes more prominent than that. We know the whole

population will not be screened. Who knows at that time point? And I also point out that even carrier screening, we've been carrier screening for CF forever, but the vast majority of babies that we diagnose with CF have not had carrier screening. So even that, there's a -- the uptake is not universal, and the only way we reach the full population at this point in time is with newborn screening. And so, I think that needs to be simply thought about from an equity standpoint as well.

And then the second thing and a lot of people have addressed this, is the impact on the programs that are actually doing the screening and the follow-up for the clinicians in that as we go through high (unintelligible) the burden increases exponentially on the programs. You know, if the multiplex stands by them, you know, it may not be that burdensome, but as we add more, if we have more reviews and they expand that, which means probably it would come through the whole Committee and at some point it probably will be added on, and it's just that, you know, if we tell a program we're adding then new conditions, I think that most programs would have a meltdown at that point, for resources, space, and personnel, and all of the programs

now are having trouble with personnel, you know, they're state based programs. Salaries are not equitable to industry and other settings, and so there are personnel shortages, there's space shortages, there are all sorts of challenges that programs are working through. And so, if you start adding many at the same time, I'm not certain how a program would be able to accomplish that.

CYNTHIA POWELL: Thank you. Sabra Anckner.

SABRA ANCKNER: Hi, Sabra Anckner, AMCHP. I just wanted to respond to Dr. Shone and clarify. I did mean what I said. So -- those choices are being made. Some of them are, you know -- I'm hesitant to call out any individual places, but you know, there is one state that funded through APHL and NewSTEPs, did Deliberative Community Engagement Process where they brought together community members to look at X-ALD, Pompe and determine if that was the right, you know, thing for that state to do, and it was determined no, and they're not screening for those things.

And you know, as a person who ran a program where I only had -- you know, we used a different lab, but I only had the option of what, you know, what our lab screened

for, but nevertheless, it was still a conversation of we are on board in this, do you want to? That is, in fact, part of the conversation, and you're looking at -- you know, and perhaps it's more of a conversation in placed with very small populations with perhaps unique ethnic makeup where you might be screening for things nobody else is screening for, as we did in Alaska, because you know, we knew what occurred in our population, and that there, you know, is not a known occurrence of another disorder.

And yeah, so I just wanted to clarify that absolutely, some of those decisions through advisory Committees, through expert panels, through conversations with commissioners, leaders, whomever, but those things are happening.

CYNTHIA POWELL: Natasha Bonhomme.

NATASHA BONHOMME: Thank you, Natasha Bonhomme. In listening to this, and I think this often happens in our conversations about newborn screening, we'll be having a conversation at what I would consider a more micro level, but the issue is actually more macro. And we keep talking about equity, and I feel like sometimes in the same breath we're saying newborn screening, you know, we get every

baby, it's equitable, but then the next thing we're saying, you're showing all the different ways that it isn't. And as long as newborn screening is completely state based and those decisions are made at that state level at different times, I don't know how fully we can say newborn screening is equitable.

And so again, I think this is, again, highlighting a system wide issue in terms of how do we define equitability, and I know we're going to have a session later on today, which is great, to really start delving into this, but we can't solve that bigger issue of it is different in different states, and there are different processes, and at the same time say we need to keep it equitable. I don't know, I don't think I'm being as direct and eloquent as I'd like to be, but I just want to highlight, we're talking about a lot of different things in this conversation. It's not just about how do we set a list of conditions that are coming in.

CYNTHIA POWELL: Thank you. Susan Tanksley.

SUSAN TANKSLEY: Hi. Susan Tanksley, Association of Public Health Laboratories. I want to start by responding to Natasha about equity and I think -- I think

it's all relative, right? So, there is the -- there's the issue of equity and newborn screening creates a more equitable situation, but it's still not -- it's still not perfect. So, more babies get screened for something if it gets put on the newborn screening panel, but then as we talked about yesterday, it creates addition issues in equity. And so it's every step of the process where we run into issues of equity, and I just -- you know, I'm glad we're -- I'm glad we're talking about it and we're raising the awareness of the issue, but I think we're -- as we evaluate it, we're going to continue to run into it, and I just -- I think it's a scale and we're going to have to -- you know, it's like we don't want to create a situation where it makes it worse. You know, it's done no harm, but everything we try to do has implications.

In response to the conversation about states and choices, you know, Scott mentioned it's a system, and it's true, within a state. Newborn screening is state based. It's not a federal mandate, however, it does feel like a mandate when a condition is placed on the RUSP, but it is -- it is a -- some states do have a process for adding conditions to their panel. And every state has a process

for adding conditions to their panel, and some of them include additional evidence review. They take information, they gather information, and they make a decision, is it right for their population? But that is not a newborn screening program person sitting down and making that decision on their own. That -- you know, that may be the Advisory Committee. That may be an entire process that's developed in a state.

Dr. Shone is absolutely right in saying that, you know, as newborn screeners, we try our hardest to do the best job we can on a daily basis and the pandemic has made our jobs exponentially harder. And we really -- you know, the things that we face on a daily basis just with staffing shortages to be able to -- and reagent shortages, and consumable shortages, to be able to do our testing on a daily basis, what we're doing now without adding something new is really hard. And so just continue -- you know, I'm sure everyone out there is facing challenges of their own from that, but please keep those things in mind, too, as we talk about those one to three years. Thank you.

CYNTHIA POWELL: Thanks. Carla Cuthbert.

CARLA CUTHBERT: Well, Scott Shone, I would like to comment on a couple of things. I'm a federal partner. I am also on the nomination and prioritization workgroup with Shawn and Scott, and you know, I want to say that I wholeheartedly support their comments. I think one of our biggest challenges, as we review this package, has been we know what we need to look for, we just can't seem to find it, and we struggle, and we struggle, and you know -- and much of it is that there is -- there is a lack of clarity within the packages that we actually get. So again, anything that allows for more complete data within the packages would be very helpful.

I have to say I like the idea of having a deadline for packages so that it doesn't sort of come out of, you know, oh, my goodness, we've got another one right now. I think that that would be nice. I do hear what Natasha said about equity and those issues, and the issues that, if you have a lot of funding going into putting in your package, you're going to have a great package. And I completely get that. And I don't know if there are ways that we can, perhaps, have better education as to the kind of data that we need that will really be able to allow us

as reviewers to be able to say yeah. They've got all of the check marks ticked. They've done it well. We can see very clearly. The evidence and the data are there, and just move it forward.

You know, there's a lot that's happening here that I really agree with. We are all stressed. And with what Sabra said with the limitations within the states, that you know, if we're having a stressful time making it through our process, the states are even having a greater challenge, and we know this because we fund the states as well, and we know that it is challenging.

I have to say that with Scott's comment about there is a lot that has to be done from the moment you actually start that clock ticking, and I appreciate that, too, because you know, when we put money out the door, we want to be able to have states pick it up, and often, as funding entities, we're in crisis when we go, but there's not enough people applying for our money, what do we do?

It's because the states have to be ready before they can say yes to the federal partners. We can take your money and we know that we can get this turned around in two years. So, I -- Scott, thank you for that, I really

appreciate what you said there. And Scott, you are awesome, and I think all other federal partners flinched a little, which not in a negative way. I just want you to know because we've had this conversation before. Are the -- you know, is it -- are the federal partners working together? Are we talking, you know? You have all of this money, are you working together in coordinating.

And again, I want to be very mindful that when we say federal partners, we're not talking about one entity with one mission, okay. We are from different agencies. We have very different missions attached to us. You know, HRSA dollars, this is not necessarily the same as CDC dollars, it's not necessarily the same as NIH dollars, and they really serve to function in different ways.

I heard the appeal yesterday when they said we need money. I know. We know that. If you know how government works, we can't say we want more money. That's really illegal for us to be able to go out and try to petition. That is definitely not okay. And we absolutely, absolutely do understand the need.

So again, I know that Michael Warren is on the call, and our other partners are on the call as well. Are

we working together? Yes, we do have conversations. We have monthly calls where we discuss where we are and what we're doing. There are certain federal partners that I have on speed dial that I run ideas by if we're thinking of certain things that we discuss. As much as we can collaborate, we would like to. It's not always easy to move dollars between agencies, or to even fund in similar ways because money is directed to different activities. But I do want you to know that we hear that call, and again, I see Michael nodding. Are we doing -- can we do more? Yes, I think that we can do more. I think that we can always do more and try to figure out ways that we can coordinate a little better. So, I do hear what you're saying, but I also want you to know that we're not -- we're not acting in isolation as federal partners. When we do have ideas, we do share it with each other, and again, working in different -- in different lanes trying to provide support to the states. So, I do want to let you know that we do hear you and we're with you in this regard, and I just wanted to offer that comment and thank you, Shawn for -- Scott -- was I saying Shawn all the time?

Scott, for what you were saying. So, I'll stop right now. Thank you.

CYNTHIA POWELL: Thank you. Michael Warren.

MICHAEL WARREN: Thank you. Michael Warren, HRSA. And thank you, Dr. Cuthbert, for your comments. I think as the Committee or the sub-group that you're putting together is thinking through this, helping also to map out where the sort of fixed parameters is. So, for example, we're in a space -- and I want to be careful as a fed not to cross a -- I will try to stick to facts. I don't want to get into an advocacy realm.

But the law is what we operate by. And so right now the current law has lapsed, but the previous law actually put into parameters around the timing by which a review had to be completed. So, once the nomination Committee moved forward and the Committee decided to move something to evidence review, the clock started ticking according to the legislation. So that's one of those parameters, I think, as the group is thinking to think through where those guard rails are.

The other gets back to the issue that you raised earlier around what are the limitations from a budget

standpoint? So, if we think about, for example, how this is funded, what line that comes from, what other things are funded out of that line and what's available for evidence reviews? Those both influence this process. And so, as the team is working through that, if there are questions that we can provide answers to, I'm happy to do that, but I think those parameters are real and important ones to consider. They're not within our purview to change. There are people who can change that. Not at HRSA, or CDC or any other federal agencies.

CYNTHIA POWELL: Max Muenke.

MAXIMILIAN MUENKE: Thank you, Dr. Powell. Maximilian Muenke. I am the CEO of the American College of Medical Genetics and Genomics. ACMG, as part of our mission is early newborn screening. And we are fortunate, and I'm grateful to the federal agencies here, I want to thank them that we are funding, we have funding for NCC that comes from HRSA, and we do the act sheets, and those -- the goal is to have Act sheets for, eventually for every newborn disorder, for every condition that's on the RUSP and expand those.

We have long term follow-up grant from HRSA. Then, of course, we have the Newborn Screening Translation Research Grant from NICHD and on top we have funding from ClinGen -- from NHDI for ClinGen. so, all of those have newborn screening. And I think the part so clearly, ACMG wants to be involved in this effort here. The part that I wanted to comment on and really appreciate Natasha Bonhomme's comment about equity, I think equity is very hard. It's very expensive and I can tell you, it's getting more expensive. And it's getting more expensive if you indulge me just to look at the scenario, what if some conditions will not be studied by a chemical in a newborn screening, but what if some will go -- will be screened by whole genome sequencing? And what I learned in the process in discussing it with companies who do this, they tell me the analysis of a genome of a person of northern European dissent is very easy, because we've had practice with it for years and years, if not decades. And it's difficult if you want to do the same thing in individuals from diverse backgrounds. So, I think we will have to be prepared if we feel equity is important, and I want to be sure to let everyone know for ACMG, equity is one of the most important

issues that we have in healthcare, and I'm very committed to equity of what ACMG can do, and at the same time, fully aware there are ethical issues there. There are funding issues there, and there are issues of possibly not having the workforce to do all of what I think we need to do to eventually have some equity that goes for all -- what is it, 3.6 million newborns in the U.S.

So, I think with that, I'm very passionate about the equity part and hope to be part of any efforts that have to do with the future of these efforts here, so thank you.

CYNTHIA POWELL: Thank you. Natasha Bonhomme.

NATASHA BONHOMME. And I appreciate the fact that this conversation has probably gone in a direction that maybe some weren't anticipating, but since we are there, I do just have to kind of call out the fact that, you know, equity isn't relative if it's impacting you and you're not getting what you need or what you feel is promised to you. So, let's -- you know, I just want us to be thoughtful about those words.

And I understand it's hard. I think we have these conversations again that, you know, we may be

thinking about, oh, what are our next steps on this, and then it turns into this big conversation, and we always get to the point of it's so hard for states and it's so hard to run these programs. And that is true. Trust me, I know. When state-based legislation is going through, I get the phone calls from people saying how can advocates think that we're going to be able to do this? So, I really appreciate that.

However, it's hard throughout this system. And I really just want us to be thinking about when we are talking about these things, that it's not just about the testing and it's not just about what's happening in the labs, but for us to really embrace, it's the entire system. And families are part of that system, too. And the slide that we keep referencing, families are at the center of that. So just really reiterating that and making sure when we are thinking about these systems and when we are thinking about different processes, then if we do have this subgroup, subcommittee, sub workgroup looking at nomination and prioritization, that we keep that in mind. It's not just a slide, it's the -- it's what we say is the core and the heart of newborn screening. Thanks.

CYNTHIA POWELL: Sabra Anckner.

SABRA ANCKNER: I just -- it's Sabra Anckner, AMCHP, and my apologies for speaking again. I just wanted to follow up to what Dr. Muenke said, which you know, to just say out loud, it's not like it's inherently easier to sequence the genome of a person from Northern Europe. These are choices that we have made. The expense that will be incurred because we have allowed and chosen to have racism build our system, that's going to cost us money because there were choices made and are still being made to focus on certain populations. We see that again in our own work, but we don't know whose psuedodeficiencies occur and we don't need a -- we're often surprised at the way that a disease presents in different populations when we -- when we implement population screening.

So, the reasons that these things are hard now is because the system is working exactly as it was intended to work historically, and to clean that up and to work on improving it is going to cost money. It's going to be hard. It's going to take time, but it also is going to require conversations like this and so I'm glad we're having it.

CYNTHIA POWELL: Thank you. Any other comments or questions? All right, I think if you could put the slides back up, we really appreciate all the comments and feedback. This will be very important as we move forward. I think, is there one more slide? Okay.

So, as I mentioned, we will be forming a workgroup comprised of current and former Committee members and other subject matter experts to develop criteria and a process for prioritizing the review of nominated conditions. The Committee will be kept apprised and will obtain their feedback throughout the process. I'm, you know, encouraged that we have a new nomination form and the materials that are now available on the HRSA website, the frequently asked questions, and other guidelines, I think the more complete the package that's submitted can be, you know, the easier the N&P workgroup work will be as well as, you know, should it go to the evidence review? You know, there are certain things we talked yesterday about, follow-up and the need to have, you know, specific thoughts from the nominators about, you know, what that follow-up will look like, both the short and long term. I think that's, you know, really critical for the nomination packages to

get some information about that because, you know, that is going to play a very important role if and when a new condition is you know, put on the RUSP, and implemented in states.

But there are certainly a lot of things that we'll need to talk about. You know, I'm getting a lot of questions from potential nominators about, you know, the difficulty in getting a newborn screening pilot for their, you know, condition done and how are we going to do that? I mean, we may be faced with conditions that have, you know, really promising treatments that are available but, you know, many advocacy groups, researchers, clinicians, clinician scientists, you know, they don't have the means to get a population based newborn screening pilot done, and so how are we going to do that. So, I hope that that's something else that this workgroup can think about because it does play a role in our ability to evaluate the nominated conditions.

So anyway, I thank you all once again for your input. Feel free to contact me with more thoughts and also Mia is available.

PUBLIC COMMENTS

CYNTHIA POWELL: So, we are a little bit ahead of time, but my understanding is those who will be giving public comments next are available.

Yesterday we received public comments specifically on newborn screening --

MIA MORRISON: Dr. Powell.

CYNTHIA POWELL: Yes.

MIA MORRISON: So sorry to interrupt. I just want to verify that we do have all of our public commenters available.

CYNTHIA POWELL: Sure. Were you able to locate Megan Pesch?

MIA MORRISON: I haven't found Megan Pesch, but you should be able to raise your hand, so we confirm if you're on, Megan. Is her hand appearing?

CYNTHIA POWELL: I'm not seeing it. So maybe we'll go ahead with, let's see, Heidi Wallis was going to be the next speaker, so.

HEIDI WALLIS: Great, good morning, hi. My name is Heidi Wallis. I'm the executive director for the Association for Creatine Deficiencies and I'm very grateful

for just a couple minutes of your time. Thank you, Dr. Kemper, for the really excellent presentation this morning.

I want to just address a couple of the things that came up and also thank you for having public comments after the presentation, it's really helpful to be able to respond on some of this right away.

First, the creatine ornithine cost for the children with GAMT deficiency and how we treat them. We did a study, the Association for Creatine Deficiencies, of the cost that most families are paying, and we looked at the CDC growth chart and the weight of children and then the recommended dosage of each supplement and we have a treatment document that I can share with the Committee members. But just to give you an idea, at two years of age the cost is $31.50 per month. So that does increase as the child grows, but in my parental opinion, I feel it's fairly reasonable.

I should add, I am the parent of two children with GAMT deficiency. My daughter was diagnosed when she was five and she is now eighteen. She is intellectually disabled and has recurring seizures, and the cost of our emergency care and our specialists care for the many

doctors she sees is way beyond our cost of supplements. So, you know, in the grand scheme of things, this cost is not even an issue, I feel.

And then as far as families getting coverage, about half of our community is able to get coverage. Some of us get this through our states that cover medical formulas, medical foods, and we work with our insurance company. It does take a lot of back and forth, but about half of our community has been able to get some coverage and support.

Another thing that came up was a comment that Utah is using an FDA kit and then running GAMT separately, and that's not correct. Utah does not use an FDA kit. They are screening GAMT with the FIA with all of their other amino acid carnatines. It is a lab developed test, not a kit.

And on that topic as well, ACD worked with the State of Utah and looked back at their cost of implementation and the estimated hours for staff for validating the test and they reagents and factored in everything, and beyond implementation the ongoing cost, and I know that this raises political, you know, pain with some

people. It is a lab developed test. It is one state's experience, so I'm not advertising this as, you know, what it will be for every state, but I think it's just a good reference to have.

The ongoing cost is estimated at 19 cents per screen, and that is a very padded estimate. It includes the labor cost of staff reviewing the additional analyte every week, any follow-up needs on a very padded number of repeats beyond what is actually seen, and I'm happy to share that document as well.

Another topic that came up is Utah's second tier and why is it being sent out? Utah initially screened for GAMT when ARUP was doing the amino acid carnatines and when tandem mass spec was brought in house, the second tier was left at ARUP. So, it's -- that is why it's out of house.

Another question was about other kinds of creatine deficiencies and could they be detected. The two other kinds are the X-linked creatine transporter deficiency. There is not conclusive research yet to identify a method for screening, so I would say no, we can't say that that could be a disorder detected by a GAMT screening.

The other disorder is somewhat similar to GAMT. It's AGAT and they've actually an AGAT patient has the reverse results with their guanidinoacetate, they would be extremely low. And right now, the lower limit, the detection of instruments tends to not be really, really great, and so it's not thought that AGAT can be picked up at this time with the screening. So, it would just be a GAMT screening.

There were some questions about false positives, and I would just throw out that these are typically NICU babies, and there's more information in the paper published, Prospective Identification by Neonatal Screening of Patients with Guanidinoacetate Methyltransferase. This was a collaboration between ARUP, the State of Utah and the State of New York, and shares all of their data very beautifully. So, I think it will -- a read over that will answer many of the questions that came up very well.

And then there was discussion about the outcomes for children diagnosed earlier and later, and that there needs to be some more documentation, some more peer reviewed papers on that and there is a sibling study being conducted right now with several different sibling pairs

where one sibling was diagnosed very early because of the older sibling, and that should be completed by the next meeting in May. So that is coming forward.

And then I just want to throw in a little bit of the reality of the disorder. Like I said, my children both have GAMT and my daughter, I recently had to do intake work for her to receive services from the State, and they asked me, you know, very basic questions, can she safely ride a bus? Could she work a job? Could she defend herself, defend her finances, defend herself physically, and I had to answer no to every single one of those questions. She is very, very much disabled being diagnosed at five-and-a-half after, you know, many years of oh, it's developmental delay, hang on, you know, just keep waiting, do these therapies. Oh, you're on the autism spectrum by one point. So, I don't know any families who have received this diagnosis in time to have a very good outcome for their child unless it's because of a sibling history.

My son is ten and he is absolutely a typical ten-year-old boy. He's very social. He's doing well in reading. He's above his grade level for reading. He does well in math. We have no problems with him. So, this is a

very important blessing for a family to receive a diagnosis from newborn screening and it truly will change lives.

And I will dip my toe in the conversation that just went on and say I -- also my background is I worked for several years with the Utah Newborn Screening Lab, so I do have some experience and some knowledge and understanding of the difficulty and challenges of implementing a new disorder, but I will say from my perspective, I look to this Committee as an advisory Committee. I think there is an obligation that if there is a disorder, that you can honestly say we advised this should be screened from birth, it meets our criteria. Although it can be very difficult for some states, I think that there's an obligation to make that advice to move that disorder forward because this is an advisory Committee creating a recommended screening panel, and it's up to each state if they follow it or not. I think the idea of asking the states if they like a disorder, if they want to screen for it, as a parent I find that very upsetting. I think it should be we have criteria, you meet it, or you don't and if you do, we advise for it. And if a state doesn't want

to, that shouldn't affect an advisory Committee or a recommendation.

So those are just my two cents from the outside view of this and thank you very much for all you're doing and thank you for your time.

CYNTHIA POWELL: Thank you. I'm told that Megan Pesch is now available.

MEGAN PESCH: Hi. Can everybody hear me, okay?

CYNTHIA POWELL: Yes.

MEGAN PESCH: Yeah? All right. Dr. Powell and Committee members, thank you for the opportunity to speak and share my perspective today. I'm an assistant professor of developmental and behavioral pediatrics at the University of Michigan and I'm also the president elect of the National CMV Foundation.

As some of you may know, along with our nominating Committee, the Foundation submitted a nomination package for your consideration of the inclusion of congenital CMV on the RUSP, and that package was submitted most recently in the fall of 2021.

As many of you may know congenital cytomegalovirus or CMV is a viral infection that's

vertically transmitted from mother to fetus, and it can be associated with adverse outcomes including sensorineural hearing loss cerebral palsy and other neuro developmental disabilities. Congenital CMV affects one in every 200 U.S. infants, which will forever blow my mind. The spectrum of outcomes is broad and thankfully, most children will have typical outcomes, but one in five will develop long term sequela, including hearing loss. And the hearing loss can develop -- can be present at birth, can be delayed in onset and is common even among those infants that are born with what is deemed as asymptomatic infections at birth.

To be completely frank, congenital CMV was not on my radar at all outside of answering board questions until late 2018 when my third daughter was born. Her name is Odessa and she looked perfectly healthy at birth, save for a few petechia on her face. She failed her newborn hearing screening, but at that time she startled when her big sisters were loud, so I wasn't worried. And frankly, at the pediatrician I had spent my career reassuring anxious moms that this hearing screen was likely a false positive.

But you can see where this is going. At two and a half months, we found out that she had by that time

profound bilateral hearing loss and at four months we found out that the etiology was congenital CMV. At that time Odessa's head ultrasound showed cysts and calcifications from the virus and because of her late diagnosis she missed that ideal window for treatment with antiviral medication, which has been found in RCT to be associated with improved hearing and developmental outcomes in the long term. But that medication needs to be started before 31 days according to the research we have right now.

And I don't want to just share my sob story. Odessa, I have a picture of her because, you know, what mom can't help. Can you even? So, she is a rambunctious preschooler now, but she has autism. She has seizures. She has bilateral cochlear implants, apraxia. She is a delight, but her life is forever changed by this disease. And you know, here's the thing. It's like I don't actually think her doctors missed anything at birth. And I mean that to say that I was staring at an infant with severe congenital CMV for months without it ever crossing my mind. Congenital CMV can't be diagnosed based on clinical presentation in the vast majority of infants. And for the

most severely affected infants, antiviral medication is a treatment option in early infancy.

And for all infants, regardless of severity, monitoring of their hearing is treatment, and they could have the opportunity to get intervention for that hearing loss should a loss develop.

Recent studies have shown that parents want to know if their child has congenital CMV even if they never end up developing sequela. And this is why I am strongly in favor of universal newborn congenital CMV screening. As with many diseases discussed in this panel, the evidence basis for CMV screening is growing. There are still gaps in the literature that need to be filled, but there is a lot of exciting work under way currently.

I look forward to your feedback on our nomination and thank you for your time.

CYNTHIA POWELL: Thank you. Next, we'll hear from Dylan Simon.

DYLAN SIMON: Thank you, Dr. Powell, and members of the Committee. On behalf of the EveryLife Foundation for Rare Diseases, I'd like to thank the Committee for providing me the opportunity to speak today to update you

on the recent newborn screening initiatives here at the foundation. Again, my name is Dylan Simon and I have the pleasure of serving as the Associate Director of Policy for the EveryLife Foundation for Rare Diseases.

The EveryLife Foundation is a non-profit, non-partisan organization dedicated to empowering these -- the rare disease patient community, advocate for impactful science driven legislation and policy that answers the equitable development of and access to life saving diagnoses, treatments, and cures.

At the current level, we (unintelligible) rare disease coalition efforts dedicated to the passage of the Newborn Screening Saves Lives Reauthorization Act. The legislation passed the House last June but is still being held up in the Senate judiciary to propose consent amendment. This is the same amendment that has been holding up the reauthorization for the last two-and-a-half years.

We are convening here as 1,000 rare disease Committee members later this month through us annul Rare Disease Week on Capitol Hill. We will meet with their

elected representatives to affect the importance of newborn screening and seek the support of legislation.

Following on this critical amendment by our advocates, we will continue to work with the rare disease community to ensure that the impact of passage of this legislation will have on the patient communities is well understood by policy makers.

We also will remain focused on shortening the timeline between when (unintelligible) added to the RUSP and screened for at the state level. Once conditions have met the evidentiary (unintelligible), the same patient organizations who led the process (unintelligible). That process requires significant resources and many more years.

The EveryLife Foundation RUSP (unintelligible) legislation ensure that states must screen for all RUSP submissions within a specified amount of time following the addition to the RUSP. Importantly, also make sure that there's a long-term planning source for the newborn screening programs to help facilitate the implementation. In the states where this legislation has passed, we work with state laboratories (unintelligible) help to make sure

that both the resource and timeline requirements meet the needs of each state program.

We have successfully passed this legislation in California, Florida, Arizona, Georgia, Ohio, and North Carolina and are currently pursuing similar legislation in Maryland, Mississippi and Iowa. I'm also happy to update that in all three of those states, legislation has been introduced in both chambers and is moving through, which we're really excited about.

Finally, we are excited to highlight that on December 29th Jack (unintelligible) network published the article Expert Evaluation Strategies to Modernize Newborn Screening System in the United States. This is a paper that Dr. Powell referenced earlier that came out with Don Bailey and the RTI team. This is a (unintelligible) study that evaluates opportunities and challenges facing the U.S. newborn screening system and presents a proposal to modernization of the cross section of experts.

The study, which was conducted again, by Don Baily of the RTI international team with support from the EveryLife Foundation by Marian Pharmaceuticals, Orchard Therapeutics, (unintelligible) Therapeutics and

(unintelligible) Therapeutics. I conclude that the next generation newborn screening system will require extensive stakeholder engagement to create community consensus, a willingness of (unintelligible) implement solutions and intensive efforts to highlight state policies and resources and ultimately national legislation.

I would like to especially thank the many of the community who participated in this study and formed this effort. As we move ahead, we are steady for the next step in this process as we work to determine how we can utilize the study, work as a community to bring about critical updates and enhancement to our newborn screening system. In 2022 we are looking forward to working with you and all leaders (unintelligible) newborn screening system.

To utilize (unintelligible) how best to modernize newborn screening. We are excited for all the great work that is occurring with the newborn screening space, looking forward to continuing to help advocates effectively navigate and engage within the community. Thank you again for your time and (unintelligible).

CYNTHIA POWELL: Thank you. Beth Vannoy.

BETH VANNOY: Hi there, good afternoon. My name is Beth Vannoy. I'm the parent of a child with metabolic disorder MCADD and the founder of the non-profit Minutes Matter MCADD. I come before you today because I know that my passion is your passion. We all share the common goal being dedicated to ensuring that all babies receive timely newborn screening so that they have the best chance to live a healthy, happy, and productive life. But the reality is, we still have work to do so that newborn screening results are timelier return to families for time sensitive disorders like MCADD.

This is evidenced by patient stories from three families that I would like to share with you today. Emory Greiser was the daughter of Patricia and Trey Greiser. Emory was the Greiser's first and only child. She was born at 1:35 a.m. on July the 15th of 2021 in the State of Maryland. At about 8:00 p.m. the next evening, July the 16th, Patricia was holding Emory. They were still in the hospital, and Emory stopped breathing.

Doctors and nurses worked on Emory for hours trying to revive her, but it was too late. Emory had suffered a metabolic crisis. Her newborn screening results

were returned three days after birth, one day too late. Emory was positive for MCADD.

Able Davis was the son of Heather and Braden Davis. Able was born on May 8th of 2020. What a sweet and joyous Mother's Day they shared at home as a family on Sunday, May the 10th, after being discharged from the hospital. But by Monday, May 11th, Heather noticed as she was nursing Able that he was not latching on well and his breathing seemed off. And within twenty minutes Able was hypoglycemic. He was rushed to the hospital. They now know, in a metabolic crisis. The crisis was too much for his little body. He passed at three days old. The next day, day four, his newborn screening results were returned. Able was positive for MCADD.

Charlotte Hall was the daughter of Emily and Theodore Hall. After a year of trying to conceive, Charlotte was born on Thursday, April the 1st of 2021. The following Monday afternoon the Halls welcomed friends and family into their home to meet Charlotte for the first time and it was during this celebration that Charlotte suffered a metabolic crisis.

She was rushed to the hospital but did not survive her crisis. Devastated and emotionally drained, the Halls were detained by the police to be questioned about the death of their seemingly healthy newborn. There were no answers.

After leaving the graveside service for Charlotte, approximately ten days after her birth, Heather looked at her phone to see that she had received a call from the UAB Metabolic Clinic. Charlotte was positive for MCADD.

I don't come here before you today claiming to have a feasible steadfast solution to this problem, but one day I will. Whether it's point of care testing for time sensitive disorders like MCADD and expedited courier service, additional state laboratories, prenatal genetic testing, we must find a solution to prevent the loss of lives and the devastation that these families have suffered. Days matter. Hour's matter and minutes matter. Thank you so much for your time today.

CYNTHIA POWELL: Thank you. And last, we'll hear from Mena Scavina.

MENA SCAVINA: Hello. Thank you and I have to say I'm a little taken aback by all the stories, so thank you for those amazing and incredible presentations.

I am a neurologist at Children's Health in Delaware and also a certified care center program advisor with Parent Project Muscular Dystrophy.

I have cared for children with Duchenne muscular dystrophy and their families for over 30 years and I'm here today to advocate for the inclusion of Duchenne testing in the RUSP. I am not a parent, so I come here from the clinical aspect. As you know, Duchenne is a progressive and fatal neuromuscular disease.

I have taken care of families with two or more boys with Duchenne. In large part this is because there was no family history. And by the time the first or the second child was diagnosed, another child had been born and later diagnosed. Had Duchenne testing been included in the newborn screening for the first child, this would have provided the parents with invaluable information for family planning.

And this has a ripple effect as well. Family members who are of childbearing age can be tested to

determine if they are a carrier. In a recent paper published in the Journal of Neurology, the mean age at first parental concern for a group of boys with Duchenne was about two-and-a-half years of age. The mean age of genetic diagnosis was about four-and-a-half years of age. And the mean diagnostic delay was approximately two years. And this supports what we see in clinic and the need for early diagnosis.

Another reason I feel strongly about the inclusion of Duchenne in the newborn screening is treatment. Until recently treatment options were limited. However, available therapies now offer more options. Exon skipping therapy to increase the level of dystrophin in the muscle is now available. Steroids and cardiac medications are being started at a much younger age than when I began practicing.

In the hope of effective gene therapy in the newborn period, as we've seen, SMA is on the horizon. With the emergence of these and other therapies, early diagnosis and initiation of therapy is necessary to change the course and the burden of disease and improve quality of life.

In addition to medical therapy, establishing a diagnosis early can lead to prompt referral to early intervention therapy such as speech, physical and occupational therapy, which are critical in early childhood development. Until very recently a state adjacent to our clinic did not include the testing for spinal muscular atrophy in their newborn screen. As a provider, I can say that not having that information readily available when evaluating a child for low muscle tone, weakness, delay, or regression of milestones required additional time and resources to carry out that genetic testing. That diagnostic odyssey can be expensive for families and having that information early on allows providers to move more efficiently through their differential diagnosis in terms of time and financial impact on the family and the medical system.

Unnecessary testing can also be avoided. I've seen many young men come through with Duchenne who underwent live biopsy. Liver enzymes are typically elevated secondary to the underlying muscle disease and elevation in the CK level. Boys are frequently referred to gastroenterologist and they undergo this liver biopsy only

to find out that it is normal, and in fact, the cause is the Duchenne muscular dystrophy.

So, I am here today to advocate for this inclusion. I look forward to a day when early diagnosis and treatment in Duchenne becomes a reality as it is already for several other metabolic muscular diseases and hopefully will be for those that were presented today because it is quite heartbreaking to hear these stories. And I thank you for your time and we look forward to your review of Duchenne nomination package in the near future. Thank you.

CYNTHIA POWELL: Thank you. Thank you to all of our speakers for sharing your experience and information with the Committee. We will now go ahead and take a break until 12:45 p.m. Eastern Time. Thank you.

(Whereupon a recess was taken.)

CYNTHIA POWELL: Welcome back everyone. We're ready to get started. For our last presentation of the meeting the Committee will hear about a preliminary analysis of the NewSTEPs quality indicator data set on health equity in newborn screening. This will be presented by Sikha Singh, who is the Deputy Director of the Newborn

Screening and Genetics Program at the Association of Public Health Laboratories.

Sikha has expertise in developing and implementing strategic work plans, mentoring personnel, advancing key partnerships, and securing funds for non-profit organizations. Sikha has been a member of the America Society of Association Executives Diversity Executive Leadership Program known as DELP and was recognized as an Association Forum 40 -- Under 40 Honoree in 2019. I'll now turn things over to Ms. Singh.

SIKHA SINGH: I shall be able to speak in just one moment.

CYNTHIA POWELL: Thank you.

SIKHA SINGH: Hi, apologies for that. Can you hear me?

CYNTHIA POWELL: Yes, we can, thank you.

SIKHA SINGH: Okay, wonderful. Thank you for that introduction and good afternoon. I'd like to thank the Committee as well as you, Dr. Powell, for inviting APHL to present today. As well as the HRSA Maternal and Health Bureau by supporting NewSTEPs.

NewSTEPs is the newborn screening technical assistance and evaluation program, and we are a program of the Association of Public Health Laboratories, and we serve as a national TA center for newborn screening laboratory and follow-up programs. One of the goals of NewSTEPs is to provide a centralized website and data repository with the intent of performing data driven outcome assessments.

Data from the repository is what we used to inform this analysis in this presentation. Specifically, I'll be talking about what the data is showing us around health equity. This discussion and discussions like it are important because centuries of racism in this country have had profound and negative impacts on communities of color, and according to the CDC, as well as according to many bodies of research, these impacts are pervasive and deeply embedded in our society.

Data show that ethnic and racial minority groups throughout the U.S. experience higher rates of illness and death across a wide range of health conditions when compared to their white counterparts. Health disparities are important to consider when establishing and

strengthening public health and clinical programs. Next slide.

So, the data that we use in this analysis were cases entered into the NewSTEPs data repository between 2011 and 2021. Next slide.

And for the time period analyzed, NewSTEPs contained just over 29,400 cases entered by 46 state newborn screening programs and it's important to note that these data were not entered uniformly by all states across the decade in which we are reporting on, and this variation is because data entry into the NewSTEPs data repository is voluntary as well as because of the fact that states are required to enter into a memorandum of understanding with APHL prior to entering the data, and that happened at various time points over the past several years. Next slide.

So, of the 35 core disorders on the Recommended Uniform Screening Panel, 16 are classified as time critical conditions and 19 are classified as time sensitive conditions. Additionally, all of the secondary conditions are also classified as time sensitive. This classification, however, certainly does not speak to the

clinical importance of the disorders or of timeliness. For example, the characterization of CCHD is not time critical. Does not mean that delays in detection and treatment of time sensitive conditions would not be detrimental.

So, of the nearly 30,000 cases that we analyzed, 3,904 conditions were time critical and 25,500 were time sensitive. Next slide.

So, this slide shows the breakdown by race and ethnicity of the cases that we examined. There were 39 different race groupings reported and about a third of the cases did not provide any race or ethnicity data. And what that tells us is that we need to figure out better ways of collecting that information. Next slide

So, for the purpose of this discussion, we examined timeliness on only those cases that were detected by the initial specimen. Next slide.

So that was about -- that was 22,199 cases distributed across the states that you see here. Again, the case entry varied across years and by state and if the case didn't indicate that -- if the case did not indicate which screen identified the risk, then those cases were excluded from the analysis. Next slide.

So, we also excluded the cases with missing timeliness data from the analysis as well as the outliers which we defined as values of either zero or having a z-score of 2.5. Next slide.

And we condensed the timeliness data into seven categories by race. Next slide.

And across the board we found that there were no significant differences by race and the timeliness of birth to collection, birth to receipt by laboratory and birth to recording. We believe that this is because of the relative uniformity of the screening across the country as an opt out program and a public health surveillance program. The differences, however, became more apparent in the buckets for median birth to diagnosis as well as birth to intervention. And these can be seen in the bar backs that you'll see on this as well as on several subsequent slides and the differences are quite visible where the differences exist. Next slide.

However, we did perform analyses to determine the significance of the differences, and we saw that there were categories that revealed significant differences between the reported racial categories. For example, timeliness

for birth to diagnosis was significantly different in black African/American babies as compared to Native American, the not reported, the Asian and white babies. And I want to note that the NO, SIR. that you'll see on this slide and subsequent slides means that the relationship was not significant but difference in the medians for time, in this case, from birth to diagnosis was not significant, meaning that they had a p value greater than .05. Next slide.

So, from birth to intervention across all race categories we saw that there were significant differences between black African American babies an all-other race. Next slide.

You then condense the race categories with the intent of having that end be fairly uniform across the categories that we condensed. And we examined the timeliness by categories of white, other mixed and not reported. And similarly, we saw significant differences in the birth to diagnosis and birth to intervention timeliness, and again, as expected, in the birth to reporting and everything analytic there was relative uniformity. Next slide.

So, what I just said about those significant differences across those three categories is also depicted here. And next slide.

We then analyzed the data by time criticality of disorders. Next slide.

So, for time critical cases we saw fewer significant differences and timeliness. Next slide.

So, for nearly all categories from birth to diagnosis there was no significant difference. And then next slide, for birth to intervention, similarly to birth to diagnosis, there were fewer significant differences across racial categories for time elapsed between birth and intervention for time critical disorders. There may be a few reasons for this. So, communication around urgent time critical disorders is strong. If a child needs to go to the ER, for example, that's a fairly straightforward directive. There's less subject to video or chance for potential health system issues to come into play when the communication says do this now, it's a life-or-death action.

Additionally, the time critical conditions are relatively panethnic and there's a dominant phase that is

affected disproportionately by those sixteen-time critical diseases, and there isn't, therefore, a racial or ancestral component to these disorders. Next slide.

So next we analyzed time sensitive disorders by race. Next slide.

And here we found that significant differences go across racial categories again. So again, I want to bring your attention to the lines on the bottom of these sets of slides and you can see that visible apparent difference, and there is, as I'll show in the following slides, still a statistical significance despite the ends in some cases being rather different. Next sidle.

So, for birth to diagnosis there was significant differences generally across all racial categories with the exception of Islander, which had a very small end. Next slide.

For birth to intervention for time sensitive disorders we, again, saw significant differences and timeliness between the black African/American babies and all other race categories, and that's denoted by the asterisks across the bottom most row. Next slide.

Finally, we performed some analyses stratified by specific disorders. Next slide.

So cystic fibrosis is predominately a disorder picked up in white babies significantly higher than all other races, however, that's not to say that other races are not impacted by cystic fibrosis. But you'll see here that in the end for white babies was 2,446 cases entered into the repository and the remaining six racial categories are rather much smaller than that. Again, you'll see with the bar graphs on the bottom there are significant differences that are being seen. Next slide.

So, what we found was that white babies were being diagnosed and receiving interventions days to weeks before black babies, other mixed babies, and Asian babies. Next slide.

Again, this slide is showing the same thing. This could be attributed to a number of things. For the diagnosis of CF there might be misconceptions like I talked about about who might have cystic fibrosis as well as issues around access. If there are only a few CF centers within a state one might run into logistical and travel

burdens that can then extend the time to achieving that intervention or even diagnosis. Next slide.

So conversely hemoglobinopathy are a disorder affecting mostly black African/American babies. And so, what we would have expected to see was that the diagnosis and intervention would be appearing more quickly for those babies, just like how would CF with the white babies realized diagnoses quicker. But that's not what we were seeing with the data here. So next slide.

So, we found no significant difference between black and white babies for the time elapse between birth and diagnosis. Next slide.

Nor did we find a significant difference across race for time elapsed from birth to intervention for hemoglobinopathy. And then we can't really be certain what to attribute this to. It could be communication or lack thereof about the urgency of this specific disease group, the impact of people not getting into clinical care fast enough and this just emphasizes the fact that ongoing education continues to be a necessary imperative. Next slide.

Finally, we examined congenital hypothyroidism, which is panethnic and it is not time critical. It often entails prolonged treatment process, and it requires going to several appointments and routine consultations with your PCP. Next slide.

So here we would have expected to see uniformity and diagnosis, but we see instead significant differences in time from birth to diagnosis between white, black, Asian, and other mixed babies. And in the next slide, you'll see that we see similar differences in time to intervention. Next slide.

So, some limitations of what we just described, what I just described was data completeness. Like I said, about a third of the cases were missing race and ethnicity data and that's a significant number. And some states did not report the screen that identified the case, so we had to bring that number of cases that we analyzed from nearly 32,000 to just over 22,000.

For data integrity and definitions, the origin of the reported race ethnicity data is unknown to us. It could come from a newborn screening kit, from the birth

defects registry, from vital records, and likely from all of the above.

We're also unclear whether the base ethnicity represents the baby or the mother. Fairly certain that it does not represent the father. And states are likely using differing definitions for diagnosis and intervention. And another limitation is race as in measure. We have to acknowledge that race is not a biological construct, it's a social construct and self-reported base does not adequately characterize the lived experience, and it does not take into account impacts associated with economic status and geography and so on. Next slide.

So, some overall conclusions that we have is that there does appear to be variations in post-analytical timeliness correlated with reported race. This was most notable in the time sensitive conditions. We acknowledge that we need better race and ethnicity data for further analyses. We can't address what we can't assess, and that harmonized diagnosis and intervention date definition used amongst programs is also necessary to enable more robust comparisons. Next slide.

And importantly, we want to thank several people, first and foremost, Amy Gaviglio, who performed these analyses and developed the content within this presentation. We would also like to thank Jelili Ojodu and Sari Edelman from APHL. Of course, HRSA, MCHB and the NewSTEPs steering Committee for routinely providing feedback to us for any number of things and most recently for the content within this presentation. And we want to acknowledge and thank the 53 U.S. Newborn Screening Programs that provide data to NewSTEPs and that every day strengthen the system and serve the most vulnerable amongst us. And on the bottom of this slide, you'll see my contact information as well as contact information for NewSTEPs, and with that, I'm happy to take any questions.

CYNTHIA POWELL: Thank you very much. We will now turn this over to questions or comments from our Committee members first and then organizational representatives. And as always, please unmute yourself and state your first and last name, use the raised hand feature. Just give folks a minute.

One question I had, are you able to separate out the cases based on whether they're from an urban home area versus rural area?

SIKHA SINGH: No, we don't have that level of information. We're only (unintelligible) state.

CYNTHIA POWELL: Okay. All right. Robert Ostrander.

ROBERT OSTRANDER: Hi there, Bob Ostrander from AAFP. And I'm really going to follow on what Dr. Powell just asked. You know, if we were doing medical research trying to look at causality of things, we would be really aware up front of potentially confounding variables and try to please those out with a number of different statistical and research means, you know, in other words, control for the other variables. I think before we draw big conclusions and more importantly before, as a society and an organization, we talk about actions to correct this. I think that really needs to happen for both socioeconomic and rural versus -- the rural versus urban variable. I mean, it undoubtedly -- I mean, in my mind I suspect a fair amount of what's driving this is socioeconomic and the socioeconomic stuff may be based on systemic racism, but

it's not systemic racism in the newborn screening programs and the healthcare delivery system per se if it's the systemic racism that causes the social disparities. It would also be interesting, you know, to know if some of those socioeconomic and social determinate issues cut across racial lines, which would be my suspicion. I mean, I live in the middle of rural western New York where we do not have a lot of diversity of color, but we have a lot of diversity of socioeconomics and I think if, you know, we took those same graphs and used the categories that we have here, I suspect we'd see very similar differences. It gets really important, again, to statistically get rid of confounding variables in this sort of thing, and especially before anybody draws any giant conclusions.

SIKHA SINGH: That's a very good point and thank you for sharing that. Certainly, I think we can acknowledge that there has been a wealth of studies conducted that do demonstrate that there are major social inequities and inherent inequities for the systemically excluded groups amongst us, and those can often be stratified by race. For this particular analysis, it's only preliminary analysis and it would be extremely helpful

if we could link to vital records and get that additional layer of information that can help better inform what this data is telling us. So those points are very well taken. Thank you.

CYNTHIA POWELL: Natasha Bonhomme.

NATASHA BONHOMME: Natasha Bonhomme, thank you so much. Thank you so much for this information and this data. I think it's critically, so thank you so much, Sikha, for presenting it, and Amy for doing the analysis, which I can't even begin to wrap my mind around.

I have a couple of things. First, an easy question. Are you planning to publish this data in any way at any point, either with further analysis or anything else?

SIKHA SINGH: Yeah, we would really like to work closely with HRSA with Amy and others who contributed to this analysis and publish something. If not formally publish it, certainly get it out there for folks to be able to access and analyze.

NATASHA BONHOMME: Great. And then my next three points I'll just go through. One is a question, you know, and I don't know if this can be answered in this setting or

just something to be thinking more about, you know, what can be done to get the data that's needed to really be able to answer this. You know, I know NewSTEPs has now a long history of working with states and getting data, but it is still a -- it's not a requirement that states provide this data and actually capturing this data is very complicated and that's not a newborn screening issue, that is a healthcare system issue. So that's one item.

Another is, you know, when we talk about time to intervention, I think it is really important either through NewSTEPs or through all the different partners to really look at what is the delay to that. I think oftentimes when we talk about, you know, lost to follow up or delay to intervention, and I don't think is done necessarily purposefully, but -- or intentionally, that's the better way of saying it, but sometimes it kind of can end up seeming like we're blaming the families, like they don't know that this is important or they don't now to come in and it is still the responsibility of the system -- I'm not saying just one group, but the system, to meet families where they are. And so, I think that -- and this isn't just a comment for this presentation, I think this is

overall when we're talking about these issues. It's not just an education on families to know how important it is to keep their babies healthy and safe. They know that. They just may not know how to do that, or they may not have gotten the message of, and this is how to do that in this instance, and that may be more education on providers or other parts of the system.

And lastly, to the comments that were just made, I agree if we can get more data and understanding those confounding issues, that would be great. But I -- and yes, socioeconomic plays a big role, but I think it's also important to know that that isn't everything. And we see that in maternal health when we know that black women who have a Ph.D. and a six-figure salary are still having worse outcomes in pregnancy, including death compared to white women who are in the Appalachian region. And that has been known for quite some time now. So yes, socioeconomics, but that isn't just it either. So again, thank you so much for this data and for us to be able to continue beyond toady to have this discussion.

SIKHA SINGH: Yeah, of course, Natasha, those are really great points. A few responses. We think that one

of the best ways to get more -- better data that can help these analyses would be by connecting to vital records and by making it easier for states to enter that data into the repository and also maybe benefitting from other HRSA funded projects for information that's collected, for example, about access to genetics, medical genetics resources stratified by a zip code, and the national data centers to do some of that work through SCMG. And then regarding meeting families where they are, this is definitely a priority. And I think that the global COVID pandemic also highlighted some of that and there have been some activities and projects. I can speak to one out of D.C. where the newborn screening outreach folks are working to develop potentially mobile solutions to help bridge the gap between those access issues that have been exacerbated or brought to late due to the global pandemic. Certainly, many of them had already been there prior to the pandemic.

And then the early hearing detection program does a really great job finding the causes of being lost to follow up and determining whether it's because of insurance coverage, access, literacy, or other things, and that's a group that we can really learn from as well, and then

target appropriately when a child does become lost to follow up.

CYNTHIA POWELL: Scott Gross.

SCOTT GROSS: Scott Gross, CDC. Thank you, Sikha. You mentioned insurance coverage. That was what I was going to ask you. Do you have any information on payer type in your survey?

SIKHA SINGH: No, in our database, we do not.

SCOTT GROSS: Because Medicaid, people on Medicaid, it's much harder to schedule follow-up visits than for people with other payer types because of lower reimbursement rates. And so, and because there's a major difference in the racial ethnic composition of Medicaid populations, that could be an important founder or a mediating variable. Thank you.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Thank you. Scott Shone, Committee member. So, Sikha, thank you so much and I probably should know the answers to this for NewSTEPs, but I wanted -- id you could just clarify a couple things on the limitations, this is coming from case data, which is separate from the stats of just routine, you know, timeliness data, right?

So, on the case data, don't those separate entries have more clarity on race ethnicity or is it carried over? And the reason I ask is I think we all know that what's on the card, any newborn screening program say what's on the card is -- I stop short of saying useless, but it's rarely -- it's often observational. There's little solicitation on Mom and as you articulated, I think you said is it Mom or babies. I think there's a lot of integrity around that question and how it's even combined on each card. Some states combine race and ethnicity under one metric, and some split it out. So first, can you just articulate a little bit on that and -- because it gets to the question of how to better get the data, and I wanted you to then say what's your vision of the vital state, because like Brendan from Texas and I think Ashley from Washington presented it on like a data a long time ago and they talked about these linkages. Is that what you're talking about, that grand or something more simplistic to poll that, and then third, can you just comment on a diagnosis and intervention date definition because I thought -- I know we used to have to establish those, so are you finding issues of programs maintaining use of those definitions?

SIKHA SINGH: Yeah, so great question. So, for -- we have three big sets of data that we collect with the new sets we have, the state profiles that tells us. The fee for a newborn screening program, what disorders you're screening, your operating hours, that public information. We then have quality indicator information and inherent within that is what we call quality indicator five on timeliness. That's aggregate data where we're looking at all of the specimens received or -- and babies, and the time that it took them from birth to collection, birth to receipt at laboratory, birth to reporting results, and then birth to intervention, and birth to confirmation of diagnosis. For those quality indicators, the term intervention and diagnosis are well defined. And acknowledging for those 35 disorders that we're collecting this information on, it could mean different things, it could be a phone call, it could be, you know, initiating medications, so on and so forth.

However, where we got this data from was that third set of data that we collect, which is the case definitions, the cases. And the race and ethnicity data for that is populated from the dried blood spot card, and

that speaks to the importance of connecting to vital records so that there is uniformity in that and there is no sort of opportunity for subjectivity, right? And then for the diagnosis and intervention for that case data, much of that information is coming back. There is feedback looped to the newborn screening program from the clinical diagnosis, and that's where that breakdown -- I don't want to say breakdown, but those differences happen in defining what a diagnosis is or defining what the intervention is because that data is coming from the clinical setting back to the program. Is that helpful?

CYNTHIA POWELL: Let's see, Debbie Freedenberg, did you put your hand down or did you?

DEBRA FREEDENBERG: I did, sorry. My question really had been related to the definition time to intervention and I think that's already been answered, because I was a little bit concerned that one state might (unintelligible) that initial telephone call saying (unintelligible) whereas another state might counsel and actually showing up in a physician's office, but I think that's been answered.

CYNTHIA POWELL: Okay. And Sabra Anckner.

SABRA ANCKNER: Hi, Sabra Anckner from AMCHP. I just wanted to just say one thing out loud, which is that not every program is reporting into this system and not thoroughly. And so, I also want us to really consider that this is basically the best-case scenario, that these are the programs that are actively working on timeliness in collaboration with APHL, that are choosing to take those steps, and the places that are collecting some amount of likely not entirely accurate race data and including it. So that, you know, I think that in itself, this is probably, if we really had data from all the programs, that it would be significantly worse, both in just overall timeliness because it would be inclusive of the places that aren't actively working on this as well as -- and the places that don't even have a way of looking at how they are performing on race and ethnicity data. So, I want to thank, you know, APHL, Sikha and the team for putting this together.

And the other thing I want to say is I really want to encourage everybody to be comfortable with this being about racism. Like it's -- you know, and I don't mean to be okay with it, but I mean, that there is not

always another reason as Natasha shared, you know, there are plenty of data points in our health system and in our system in general that show that the factor is race when you exclude everything else. And there is not a reason to believe that the newborn screening system would be -- exclude itself from that, that somehow it would be magically not be influenced by these things that we know impact health outcomes and infant health outcomes, and all of these other things, you know, socioeconomics, status, where you live, all of those things also impact, but race by itself and in and of itself consistently is a predictor of health outcomes. And I really -- if we can't embrace that, if we can't accept it as a systems issue, then we can't address it.

SIKHA SINGH: Yeah. That's really -- that point is well taken for the 29,400 cases that we looked at over that decade of time, that data came from 46 states and there is a fairly good amount of representation, however, not every state entered all the data for the entire decade and so on. And we certainly can't say that the states who didn't provide that data are not also working on timeliness

or doing other things, so there is that spectrum, but you definitely make good points. Thank you for sharing that.

CYNTHIA POWELL: Robert Ostrander.

ROBERT OSTRANDER: Yeah, Bob Ostrander at AAFP. I wanted to make sure everybody is clear that I wasn't looking to explain away the role of race in what's going on because that clearly wasn't the case. It's just a matter of when I'm thinking about things in terms of possible solutions, I really think of it like I would a medical problem and knowing what the contributors are and what the magnitude of the contributors are helps to find the solution. And I think, you know, that's kind of my patch is that we make sure we do that. Because honestly, some of the -- you know, some of the non-directly racism as opposed to indirectly racism things may have a more direct solution and potentially might, you know, in certain situations be playing a bigger role. So, you know, I wouldn't ever want anybody to think my comments were -- I don't want this to deteriorate into a political discussion about whether folks were trying to deny the existence of racial disparities even when all the other variables are controlled for it. You know, that's clearly the case. But I still think when

you're looking to solve problems you need to know what the magnitude of each contribution is in designing your solutions.

CYNTHIA POWELL: Thanks.

SINKA SINGH: And I just wanted to say we didn't take it that way. Certainly, the entire picture is very important. Race is not the only factor to consider, albeit it's a very important one, but thank you for sharing that.

CYNTHIA POWELL: And before we wrap up, I just wanted to see if Scott Gross could provide some additional information regarding the statement about Medicaid patients having a more difficult time to get follow-up, if he's still --

SCOTT GROSS: Yes.

CYNTHIA POWELL: Go ahead.

SCOTT GROSS: There was actually -- multiple studies have documented this, but the most interesting are valuations of the policy experiment. It's resulted in the Affordable Care Act. In 2013 and 2014 Medicaid programs were required to reimburse at the same level as Medicare. Usually, most state Medicaid programs have substantially lower reimbursements than Medicare rates, and it becomes

financially hard for clinics that have a lot of Medicaid patients. And so, it's understandable why clinics might be more reluctant to schedule this. And what these studies have shown is that when Medicaid reimbursements were set equal to the Medicare rates, the number -- why people covered by Medicaid rose substantially.

CYNTHIA POWELL: So, it's really that the providers are not wanting to take Medicaid patients because of the poor reimbursement?

SCOTT GROSS: I would say providers, I would say -- it's an institutional, not the individual providers.

CYNTHIA POWELL: Uh-huh.

SHAWN MCCANDLESS: Scott, Shawn McCandless. Did those data specifically address neonates or infants?

SCOTT GROSS: No. No, this is -- no, different age group.

SHAWN MCCANDLESS: Yeah. And I'm a little bit concerned about extrapolating from one age group to another because certainly what we see locally is that the institutions that primarily provide care for adults have very different policies about accepting Medicaid patients

than do the institutions that provide care for children and infants.

SCOTT GROSS: I think I do recall years ago there was one study which looked specifically at the impact on children with special healthcare needs. I'll have to look that -- pull that one out and share it with you, Shawn.

CYNTHIA POWELL: All right. Well, Ms. Singh, thank you so much for your presentation today. Clearly, it's an area of great interest and, you know, we look forward to hopefully updated data as you're able to acquire them in the future.

All right. Now we'll have a few minutes if there's new business and I think Natasha Bonhomme had a couple of things she wanted to bring up.

NATASHA BONHOMME: Thank you so much, Dr. Powell. First, I wanted to let the Committee know that through Babies First Test we are convening a workgroup looking at newborn screening and CCMV. This is done in partnership with the CMV Foundation, and we are really happy that on that group we have about 30 people, 10 of which are representing 10 different states and we will have our -- we've had numerous one on one conversations. We will have

our first meeting in March. And really the purpose of this workgroup is really to build bridges between the CMV community and the newborn screening community as they -- and really discussing together critical issues when thinking about implementation. If there's anything that comes out of that workgroup that would be of interest to this Committee, we are happy to share that in any way that is appropriate and helpful. And so, I wanted to mention that.

And secondly, I wanted to take the time to acknowledge the amazing work of Joan Scott, who is retiring. I have -- I feel very lucky that she -- I met her at the very beginning of my career in this work and learned from her about focus groups and you know, really getting public perspectives on genetics. That was during her time at the Genetics and Public Policy Center, but I just wanted to take a moment to acknowledge all of her work and effort in this base and to say thank you. Thanks.

CYNTHIA POWELL: Thank you for bringing that up. Yes, Joan Scott has already retired. Unfortunately, as far as I know she wasn't able to join this meeting, but I certainly echo your sentiments, Natasha, and having known

Joan since we were graduate students together, I have always been so impressed by all that she's done and accomplished and thank her for all the help as I've served on this Committee over the years. So, thanks for acknowledging her.

ADJOURNMENT

Anyone else with any new business? All right, hearing none, our next meeting will be May 12th through 13th, and I am told unfortunately, that's going to likely be another virtual meeting. But we look forward to getting together again. As noted earlier, we will be putting together the workgroup to look at the possibility of prioritizing applications and I appreciate those who have contacted me already, you know, stating your interest in doing that, we'll get back to you. And if nothing else, we'll adjourn this meeting. Thank you all.