The Advisory Committee on Heritable Disorders in Newborns and Children

Virtual Meeting

10:00 a.m.

Thursday, August 12, 2021

Attended Via Webinar

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Reported by Garrett Lorman

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Melissa Parisi, MD, PhD

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C O N T E N T S

P R O C E E D I N G S

WELCOME, ROLL CALL, OPENING REMARKS, COMMITTEE BUSINESS

CYNTHIA POWELL: Good morning, everyone. I'd like to welcome everyone and call to order the third meeting in 2021 of the Advisory Committee on Heritable Disorders in Newborns and Children. I'm Dr. Cynthia Powell, Committee Chair.

I'd like to begin by first taking roll of our Committee Members representing the Agency for Health Care, Research, and Quality, Kamila Mistry.

KAMILA MISTRY: Here.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Here.

CYNTHIA POWELL: Jeff Brosco. I believe Jeff is going to try to join later on today.

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: Here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: Representing the Centers for Disease Control and Prevention, Carla Cuthbert.

CARLA CUTHBERT: I'm here.

CYNTHIA POWELL: Representing the Food and Drug Administration, Kellie Kelm.

KELLIE KELM: Here.

CYNTHIA POWELL: Representing Health Resources and Services Administration, Michael Warren. Joan, are you our -- Joan Scott, are you representing --

JOAN SCOTT: Yes, I'm here, although I am expecting Dr. Warren any -- any minute.

CYNTHIA POWELL: Okay, thanks. Shawn McCandless.

SHAWN MCCANDLESS: Here.

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

MELISSA PARISI: Here.

CYNTHIA POWELL: I'm here. Annamarie Saarinen. Scott Shone.

SCOTT SHONE: Here.

CYNTHIA POWELL: Next, our organizational representatives. From the American Academy of Family Physicians, Robert Ostrander.

ROBERT OSTRANDER: Here.

CYNTHIA POWELL: And the American Academy of Pediatrics, Debra Freedenberg.

DEBRA FREEDENBERG: Here.

CYNTHIA POWELL: From the American College of Medical Genetics, Maximilian Muenke.

MAXIMILIAN MUENKE: Here.

CYNTHIA POWELL: From the American College of Obstetricians and Gynecologists, Steven Ralston. From the Association of Maternal and Child Health Programs, Jed Miller.

JED MILLER: Here.

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

SUSAN TANKSLEY: Here.

CYNTHIA POWELL: From the Association of State and Territorial Health Officials, Chris Kus.

CHRISTOPHER KUS: Here.

CYNTHIA POWELL: From the Association of Women's Health, Obstetric, and Neonatal Nurses, Shakira Henderson. From the Child Neurology Society, Jennifer Kwon.

JENNIFER KWON: Here.

CYNTHIA POWELL: From the Department of Defense, Jacob Hogue.

JACOB HOGUE: Here.

CYNTHIA POWELL: From the 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: Here.

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

GERARD BERRY: Here.

CYNTHIA POWELL: Thank you. I'll next turn things over to our Designated Federal Official, Mia Morrison.

MIA MORRISON: Thanks, Dr. Powell. Next slide, please. So, I'll now go over a few standard reminders for the Committee. As a Committee, we are advisory to the Secretary of Health and Human Services, not the Congress. For anyone associated with the Committee or due to your membership on the Committee, if you received inquiries about ACHDNC, please let Dr. Powell

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

When a vote is scheduled or an activity is proposed and you have a question about a potential conflict of interest, please notify me immediately. Next slide.

According to FACA, all Committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register and/or announced at the opening of the meeting. For the August meeting in the Federal Register notice, we said that there would be a public comment period. Only with advanced approval of the chair or DFO, public participants may question Committee Members or other presenters. Public participants may also submit written statements. Public participants should be advised that Committee Members are given copies of all written statements that they submit. As a reminder, as stated in the FRN as well as the registry website that all written public comments are part of the official meeting record and are shared with Committee Members. Any further public participation will be solely at the discretion of the chair and DFO.

And if there are no questions, I'll turn it back over to Dr. Powell.

CYNTHIA POWELL: Thank you, Mia.

For our first item of Committee business, I'd like to announce that Dr. Gerard Berry will replace Dr. Georgianne Arnold as the organizational representative for the Society of Inherited Metabolic Disorders. Dr. Berry is a biochemical geneticist and pediatric endocrinologist. He is the Harvey Levy Chair in Metabolism and Director of the Metabolism Program at Boston Children's Hospital, Professor of Pediatrics at the Harvard Medical School, and Director of the Harvard Medical School Biochemical Genetics Training Program. Dr. Berry is the President of the Society for Inherited Metabolic Disorders. He is the co-chair for the Metabolomics Working Group of the NIH Undiagnosed Diseases Network. His review panel and other NIH service work included serving as a member of Gene Therapy and Inborn Errors Special Emphasis Panel and the chairman of the Rare Diseases Clinical Research Network Data.

Dr. Berry's primary clinical and basic science research efforts are focused on galactosemia and secondarily on myoinositol metabolism in the brain, particularly during fetal development.

Dr. Berry, we are very excited to welcome you, and Dr. Arnold, we thank you for your contributions to the Committee.

GERARD BUTLER: Glad to be here. Thank you so much, Cynthia.

CYNTHIA POWELL: Thank you. All right. Next slide, please.

First, I'd like to inform the Committee that in July, HRSA received a nomination package for Krabbe Disease or Globoid Cell Leukodystrophy. Krabbe Disease is both a leukodystrophy and a lysosomal storage disorder and was first nominated to the Advisory Committee in 2007. It went through evidence-based

review; however, in 2009, the Committee voted to not recommend addition to the Recommended Uniform Screening Panel.

HRSA is in the process of conducting the initial review for completeness and will keep the Committee informed of next steps.

We are working towards finalizing the effort to review the evidence review process. This has been an ongoing endeavor that began in February of 2019 when the Committee convened an expert advisory panel to explore ways to strengthen the nomination and evidence review process. Since then, the Committee has provided their feedback and expertise to identify the feasible next steps. Today, Dr. Alex Kemper and I will present an overview of the process and the proposed updates. The Committee will vote on whether or not to approve the proposed updates at the November 2021 meeting.

As a reminder for groups that may be in the process of developing condition nomination packages, the new processes will not go into effect until calendar year 2022. If your organization is working on a condition nomination package and you are planning to submit in early 2022, please contact the Committee's Designated Federal Official, Mia Morrison, who can provide you with additional guidance. Mia and I are available to provide technical assistance to nominators. Next slide.

Next, I would like to announce that there is an opportunity for public comment on the proposed data collection activities for the Public Health System Assessment Surveys. The purpose of the Public Health System Assessment Survey is to inform the Advisory Committee on states' ability to add newborn screening for nominated conditions including the feasibility, readiness, and overall capacity to screen for new conditions. The complete announcement was published on

July 22, 2021 in the Federal Register. If you would like to look it up, the document citation is 86FR38726. The only proposed changes to the survey instruments are grammatical. You may submit your comments on the survey to paperwork@hrsa.gov. There is also a mailing address listed in the Federal Register. Comments must be received no later than September 20, 2021. Please continue to monitor the Federal Register for additional information and updates. Next slide, please.

Thank you to the Committee and organizational representatives for reviewing the May 2021 Meeting Summary. We received one edit that the Committee has not had a chance to review. On page 4, organizational representative Natasha Bonhomme's title has been corrected to Founder of Expecting Health.

Does anyone have any additional corrections at this time before the Committee votes? Hearing none, do I have a motion to approve the minutes for the May 2021 ACHDNC meeting?

ANNAMARIE SAARINEN: So moved, Annamarie Saarinen.

CYNTHIA POWELL: Is there a second?

KYLE BROTHERS: Kyle Brothers, second.

CYNTHIA POWELL: Thank you. We'll now take a vote about approving the May 2021 Minutes. Mei Baker.

MEI BAKER: Approved.

CYNTHIA POWELL: Jeff Brosco. He's not here. Kyle Brothers.

KYLE BROTHERS: Approve.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: Approve.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Approve.

CYNTHIA POWELL: Kellie Kelm.

KELLIE KELM: Approve.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Approve.

CYNTHIA POWELL: Kamala Mistry.

KAMALA MISTRY: Approve.

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Approve.

CYNTHIA POWELL: I approve. Annamarie Saarinen.

ANNAMARIE SAARINEN: Approve.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Approve.

CYNTHIA POWELL: Michael Warren.

MICHAEL WARREN: Approve.

CYNTHIA POWELL: Thank you. So, the motion is passed for approval of the minutes. May I have the next slide, please.

Today, we have a very packed and I think exciting agenda. The Committee will meet today until 2:30 p.m. Eastern time. First up, the Committee will have Dr. Alex Kemper provide the Phase 1 update of the evidence-based review for Mucopolysaccharidosis Type II or MPS II. Next, Dr. Kemper and I will provide an overview of the Committee's review of the Evidence Review Process and present on proposed updates. Afterwards, we'll have a public comment period. Nine individuals have registered to provide an oral public comment to the Committee today. Our first group will

give statements on a nomination of guanidino acetate methyltransferase deficiency or GAMT Deficiency to the Recommended Uniform Screening Panel. They are Kim Tuminello and Heidi Wallis from the Association of Creatinine Deficiencies, Dr. Nicola Longo and Dr. Marzia Pasquali and Becky and Stu Tribe.

Afterwards, we will hear from Dr. Joanne Kurtzberg who will discuss Krabbe Disease, Elisa Seeger, who will provide comments on the Committee's review of its processes, Dean Suhr from the MLD Foundation, who will also provide comments on the Committee's review of its processes. Our last public commenter will be Liesle Broadridge from the EveryLife Foundation for Rare Disease, who will discuss the Third Annual Newborn Screening Boot Camp.

Following the public comment period, the Committee will take a 30-minute break and reconvene at 1:15.

After the break, the Nomination and Prioritization Work Group will provide a summary of the nomination package for GAMT deficiency. Immediately after the Nomination and Priority Work Group Presentation, the Committee will have an opportunity to discuss the nomination package and hold a vote on whether or not to move GAMT deficiency forward to full evidence review.

The last session of today will be a Committee discussion on emerging issues in newborn screening led by Committee Member, Dr. Shawn McCandless. Next slide.

The Committee will reconvene tomorrow, Friday, August 13th, from 10:00 a.m. to 1:50 p.m. Eastern time. We will begin tomorrow with a panel on National Registries for Hemophilia and Childhood Cancer and thinking about how this may help in terms of follow-up

of patients with conditions detected through newborn screening as we've done in the past.

Our final session of the August meeting will be a panel continuing the Committee's exploration of the Newborn Screening Workforce with a focus on laboratory and follow-up, audiology, pediatric endocrinology, and genetic metabolic dieticians.

I'll now turn it back over to Mia.

MIA MORRISON: Thanks, Dr. Powell. Next slide, please.

So, member of the public, audio will come through your speakers. So, please make sure that you 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 number in the email with your Zoom link. This meeting will not have a chat feature, but we do have a public comment period scheduled later today.

Committee Members and organizational representatives, audio will also come from your computer speakers, and you will be able to speak using your computer microphone. If you can't access the audio microphone through your computer, you may dial into the meeting using the telephone number in the email with your user-specific link sent to you from Vincent Levin. Please speak clearly and remember to state your name first to insure proper recording for the Committee transcript and minutes. The chair will call on Committee Members first 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 questions. Simply click on the participant icon and choose raise hand. Please note that depending on

your device or operating system, the raise hand function may be in a different location. 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 taskbar. From that menu, you may select show subtitles.

I will now turn it back over to Dr. Powell.

CYNTHIA POWELL: Thank you, Mia. May I have the next slide, please. Next slide.

As you might recall, at the May 2021 Committee meeting, the Committee voted to move Mucopolysaccharidosis Type II or MPS II to full evidence-based review. Starting in May, the Committee has nine months to complete the evidence-based review and vote on whether or not to recommend MPS II for addition to the Recommended Uniform Screening Panel.

Today, Dr. Alex Kemper, lead of the evidenced-based review group, will provide the Phase 1 Update for the MPS II Evidence Review. Dr. Kemper is the Division Chief of Primary Care Pediatrics at Nationwide Children's Hospital and Professor of Pediatrics at the Ohio State University College of Medicine. He completed his pediatric residency training at Duke University followed by combined fellowship training in health sciences research and medical informatics with residency training in preventive medicine at the University of North Carolina. Dr. Kemper's research focuses on the delivery of preventive care services including newborn screening. Since 2013, Dr. Kemper has also served as the deputy editor of Pediatrics. I'll now turn it over to Dr. Kemper.

MUCOPOLYSACCHARIDOSIS TYPE II (MPS II) EVIDENCE REVIEW - PHASE 1 UPDATE

ALEX KEMPER: Dr. Powell, thank you very much for that kind introduction and I'm really excited on behalf of our Evidence Review Group to present our first interim presentation around newborn screening for Mucopolysaccharidosis Type II or MPS II.

The purpose of this presentation is to raise some high-level points that we've learned so far around MPS II, to talk about our ongoing process for the review, and also give the Advisory Committee another opportunity to bring up issues or points that they would like us to further explore as we go about our work on MPS II. Next slide, please.

So, this just lists our team members. I'm very fortunate to be able to work with a wide range of really smart and invested individuals and I'll just leave that for a second to give them due credit. Next slide, please.

We have also convened a technical expert panel. As members of the Advisory Committee may recall, we used the technical expert panel to help guide us throughout the review process to make sure that we understand issues related to the conditions, to explore whether or not there are important unpublished data that could be used to inform the decision and our review process and really to make sure that we understand the condition in the appropriate context. The technical expert panel includes researchers, clinicians, and individuals who have firsthand experience with conditions. So, we're very fortunate again in this case that we have a very strong technical expert panel. Next slide, please.

So, just reminding the Advisory Committee, this slide presents the -- the timeline under which we're operating. So, back at the May meeting was when the

condition was nominated. We had this interim presentation, another interim presentation in November, and then our final presentation will be coming up in February. Hopefully the pandemic will resolve and maybe we can even meet in-person. Next slide.

So, now I just wanted to get a little into MPS II. So, in terms of our case definition, MPS II is an X-linked lysosomal inborn error metabolism caused by the deficiency of the specific enzyme leading to accumulation of specific glycosaminoglycans or GAGS, as you'll see on subsequent slides. There are many, many mutations associated with the IDS gene. A lot of these mutations are private mutations, which, as you'll see in a little bit, can be challenging in terms of predicting the phenotype.

Across reports we've looked at, there's a fairly wide range of prevalence based on clinically detected cases ranging from 0.2 per 100,000 live births up to 2.5 per 100,000 live births. If you look at the states that are screening for MPS II, Illinois had found about 0.88 cases per 100,000 live births and Missouri 1.37 per 100,000 live births through newborn screening. Again, I hope these numbers just give a sense of the prevalence as I talk about the condition itself. Next slide, please.

So, the classification of MPS II is a little complicated, and it bears spending some time thinking through it because as we talk about what we've learned related to presentation, understanding how cases are described, I think, is really important.

So, there is one classification of severe versus attenuated disease and that's based on the degree of involvement. But the attenuated term is to me a little bit of a misnomer because attenuated implies that it's -- that the cases aren't just severely affected and that's not true. So, as a key

point, attenuated is not the same as benign and I'm going to dig into what these various presentations are in a little bit.

There's another classification where cases are described as neuronopathic versus non-neuronopathic; neuronopathic referring to CNS involvement. But individuals who have non-neuronopathic disease can actually have CNS involvement related to the degree of involvement, for example, the spinal cord and those kinds of things. And so, it's a little bit of a misnomer to think that there's no CNS involvement in those with non-neuronopathic disease. And so, it's important to think that individuals who have MPS II can have variable phenotypic expression across disease dimensions.

Again, to really drive home the point, I just want everyone to remember the attenuated is not the same as benign and non-neuronopathic is not the same as no neurologic involvement. Next slide, please.

So, in terms of separating out severe versus attenuated disease, severe disease typically has progressive multi-organ and joint involvement as these GAGs accumulate. Not only can there be cognitive impairment, but also regression. The diagnosis is typically in early childhood with death occurring during the late teen years or in the 20s. One thing that is important as we talk about screening is that, at least based on clinical detection, most cases are thought to be severe -- two-thirds of the cases. Attenuated disease typically has a later diagnosis, but as with severe disease, can have progressive multi-organ involvement. These individuals can live into adulthood, but from talking to members of our technical expert panel, the later death is because there's not this same degree of CNS comorbidity. Again, I want to drive home the point that the attenuated disease is not

the same as benign and there is this wide spectrum of disease.

As with many of the other conditions that we've considered, there is also pseudodeficiency. Pseudodeficiency is not associated with morbidity or mortality. There's ways to rule out pseudodeficiency and I'm going to talk about this in a little bit, essentially looking at whether or not there's a high level of GAGs in the blood and can therefore be ruled out to avoid concerns of unnecessary treatment.

Another point that's important to remember is that the phenotype is not typically predictable at the time of diagnosis because there's so many private mutations. What we've heard from the experts and what seems to be going out by the articles that we've looked at thus far is that affected siblings generally have similar phenotype. The severe form can be predicted if there's a complete deletion or major complex rearrangement. What I can't tell you yet is the proportion of cases that are due to these complete deletions or complex rearrangements and hopefully at our next presentation, we'll have more information about that.

But again, the phenotypic prediction isn't typically possible for the private mutations -- the new ones that have developed. Next slide, please.

So, in terms of screening, there's really two approaches that can be used, and these are all based on measuring enzyme activity. There's tandem mass spec assay which can be multiplexed with other markers for other lysosomal storage disorders, for example. And I put a reference on the slides too for the method that is generally used. But it's using this UPLC with tandem mass spectrometry. I'm going to dig a little bit more into the methods on a subsequent slide.

The other method if a microplate fluorometric assay, which is not multiplexed. From speaking to the two states that are using each -- again, I'm going to dig into this in a second using a different method -- the individuals in the newborn screening laboratory have noted that there does seem to be a clear separation between positive and negative screens at the time of screening, which, you know, obviously has a lot of benefit.

After a positive screen in terms of working up to confirm the diagnosis, the first step is to confirm enzyme activity to measure GAGs. Pseudodeficiency would not be associated with elevated GAGs. And then sequencing of the gene can be helpful, but again, these are all private mutations and are not necessarily going to tell you what the phenotype is.

There is another very rare condition, Multiple Sulfatase Deficiency, that can be ruled out by measuring another sulfatase during the diagnostic evaluation. But the key elements are really confirming the enzymatic activity and doing the GAG measurements. And I'm going to explore in subsequent slides how states -- the two states that are screening handle this a little bit differently. Next slide, please.

So, in terms of treatment, there is enzyme replacement therapy, Idursulfase. This was approved back in 2006 and it's really become the standard of therapy. It's -- it's delivered by IV infusion and the infusion itself can take many hours to give. So, some individuals may get a permanent indwelling catheter for the infusion and others, you know, for whatever reason may opt to have an IV put in each time. But regardless, it is delivered by IV infusion.

A key point to remember, we're going to be coming back to this a couple times, is that the enzyme replacement does not cross the blood-brain barrier. As

we've seen with other enzyme replacement therapies, there is a risk of developing antibodies to the enzyme replacement therapy. We are still in the evidence review process in determining how big of a problem that is in terms of affecting or impacting the effectiveness of the enzyme replacement therapy. Again, I won't be surprised if there are also the risks of infusion-related side effects -- rash, angioedema, and so forth, and this could be rerated with cream and medication, sometimes slowing down the rate of the infusion -- the standard things that we've seen.

There is a study going on right now that's evaluating the role of intrathecal administration for individuals who have CNS involvement and just by way of background, the cost of the enzyme replacement therapy and the administration of it is on the order of hundreds of thousands of dollars per year.

The other therapy for MPS II is hematopoietic stem cell transplantation. This is really not a major component of therapy. Certainly after enzyme replacement therapy became available, it was really -- enzyme replacement therapy really supplanted the use of stem cell therapy because of the risk of mortality and also -- and this was pointed out from our technical expert panel -- the lack of clear neurodevelopmental benefit of stem cell transplantation, which -- which does seem to be in contrast to what we saw with our previous review of MPS I. Again, we're now looking at the published evidence to get a better sense of this.

Again, it's, you know, some families might prefer stem cell transplant because it could potentially avoid the need for those weekly IV infusions. But from what our experts have said, families have generally preferred or nearly always prefer the enzyme replacement therapy.

MPS II is a really active area of research including some exciting work that's going on around gene therapy. We are now just in the process of figuring out what these novel approaches are, where those studies stand, you know, given the rarity of MPS II, it may be hard to fill those studies, especially if there are competing trial underway.

So, again, by the time the final vote comes out, we are unlikely to have a lot of new information about these novel therapies. But they are in development, which is obviously very exciting. Next slide, please.

So, the clinical experts from our technical expert panel said that they recommend beginning the enzyme replacement therapy as soon as possible after diagnosis. Again, there is a strong biological argument that enzyme replacement therapy can stop accumulation of GAGs, but once the GAGs have already developed, the general thinking is that the damage has been done.

The enzyme replacement therapy itself was approved about 15 years ago based again on studies of mostly clinically detected subjects where, you know, some subjects could be detected if they had an affected sibling.

Now, I do want to highlight something that's on the drug label. I think it's important to understand why it's on the drug label and what the new evidence is that's come out since then. And I really want to highlight that the drug label was done at the time of approval, which, you know, again was about fifteen years ago. So, the label states, "In patients 16 months to 5 years old, ELAPRASE (which is the brand name) did not show improvement in disease-related symptoms or long-term clinical result; however, treatment with ELAPRASE has reduced spleen size

similarly to patients 5 years and older. It is not know if ELAPRASE is safe and effective in children under 16 months old."

So, if you were to just look at that labeling, it would, you know, potentially raise concern about newborn screening and beginning therapy, you know, very soon after identification. But I think it's important for the Advisory Committee to recommend that there have been post-marketing studies since then, additional observational studies, and a lot more clinical experience since that -- since the drug was approved by the FDA. Next slide.

So, the technical expert panel pointed out that there's a lack of equipoise at this point for the kind of trials that might be needed to substantially change the label. Again, I mentioned the biological argument about treatment after the GAGs have accumulated not reversing tissue damage, but given the -- the time horizon over which MPS II develops, measuring meaningful outcomes takes longer than the duration of typical clinical trials, you know, over, you know, we're talking about like a condition without treatment can present with the joint tissues or problems walking or the neurodevelopment issues that we talked about before over many years and then there are also post-marketing studies that support the safety of presymptomatic treatment.

So, even -- and of course, given the rarity of the disease, beyond the issue of equipoise, enrolling subjects for early treatment or other novel therapies in the absence of screening is-- is going to be a barrier. I recognize that -- that newborn screening is not done to identify subjects for trials, and that's what -- I don't mean to imply that. But I do think that it's important to understand that getting

sufficient subjects for things like label change is difficult. Next slide.

So, in -- in this vein, I just wanted to highlight one study -- and there are other studies that describe issues of safety in enzyme replacement therapy in younger children -- this is one particularly study and you can see the reference below of twenty subjects between 1.4 and 7.4 years in an open-label study. There is one subject who was unenrolled because the individual wasn't compliant with enzyme replacement therapy. I can't comment on why that happened. A substantial proportion developed IgG antibodies. I don't know how that effected the -- how that impacted the effectiveness of therapy and about half of the subjects had infusion-related adverse events. But all of these subjects were able to continue with therapy and, you know, I think that's a key thing for the Advisory Committee to consider. Next slide.

And I do, you know, there are many studies on enzyme replacement therapy begun early versus late in siblings. I think this one particular study because they were friends of the two children and I think that's helpful. So, this was a study of one child as she began enzyme replacement therapy at 3 years of age. He was detected clinically. You can see a picture of him on the left and then his sibling, who began therapy at 4 months of age, and you can see him on the right. And after about 30 months of therapy, you can see the, you know, differences in the facial appearance. There are differences between the siblings in terms of joint stiffness, hepatosplenomegaly. Both of them had intellectual disability but were differentially impacted. You can see the one who is a bit older had a development quotient of 42 versus 74. You know, there's only so much you can draw from an observational study of two siblings since I don't know why the developmental quotient was so different between the two

of them. Classically speaking -- not classically speaking, we know this, enzyme replacement does not cross the blood-brain barrier, but, you know, in discussing this with the technical expert panel and amongst our group as well, you can imagine that because the child that was picked up earlier was able, you know, didn't have the joint stiffness and many other side effects -- many of the other adverse issues associated with MPS II, might have gotten better stimulation and maybe that accounts for some of the differences in the developmental quotient.

Again, we'll be able to explore this more in the published and unpublished literature. Next slide.

So, I just want to highlight now some important sources of data. First of all, there's the Hunter Outcome Survey, which includes now more than 1,000 individuals with MPS II. It's used both to describe the natural history as well as has some individuals who, you know, began treatment at various times in their life. There is a parent- or patient-reported functional outcomes survey that's in here as well as other metrics of how the subjects are doing. This was supported by Shire. I can tell you there are many, many publications that have come out of the Hunter Outcome Survey, which has really great insight into the condition.

There are two states -- only two right now -- that screen for MPS II, Missouri, which began in 2018 and Illinois, which began in 2017.

ScreenPlus, which is a study of screening for various conditions, includes MPS II. We spoke to Dr. Orsini in New York about ScreenPlus just the other day. They've been a little bit slow to get started because of, you know, issues with the pandemic and just the complexity of the study. So, we don't have anything to

report in terms of cases that they've identified. But I will have like the method that they use.

Taiwan has been screening for a relatively long period of time, since 2015. And then another important source of data, but I'm not going to drill into more here, are open-label and uncontrolled trials of enzyme replacement therapy. Next slide, please.

So, let's talk a little bit about Missouri first. So, they began full population screening back in 2018. They used a benchtop fluorometric test. Again, they have in their first-tier assay, they seem to be able to easily separate positives from negatives. They told us that it takes about two hours to prepare the samples and read the plates, and on top of that, there's three to four hours of time to run the assay. Again, this is not multiplex.

They told us on our first call with them that the unit screening cost for MPS II is about $5 including things like staff time, equipment and overhead, and those sorts of things. I -- I, you know, hesitate to put that $5 number out until we're able to better explore exactly what's in there and what's not and Dr. Scott Grosse, a member of our group who is at the CDC -- everyone knows Scott anyway -- is working with us right now to better sort out what's in that cost. But I think that $5 number is -- is helpful at least to give you an idea of what they have told us.

They do GAG testing as a send-out lab prior to referring for specialty care, and they found that the molecular second-tier testing wasn't particularly helpful. I am working with them to really get the numbers at each step in the algorithm and to really understand exactly, you know, what they found and the number of cases detected. Next slide, please.

But for the purposes of this slide, I just wanted to highlight that they are not multiplexed and they have the second-tier test of GAGs that are sent to the Mayo for measurement and then referral is made. So, that's a way to sort out pseudodeficiency prior to referral. Next slide, please.

So, looking at just the 2020 numbers, they screened about 86,000 newborns and found 20 with pseudodeficiency -- again, that was prior to referral -- and 12 had been referred, meaning that, you know, if all the referred cases turned out to have MPS II, that's a potential as much as 14 per 100,000 cases. We are working with them to get all the numbers and then go back for 2020. So again, I just give you this as a flavor of what's to come. They have not found any affected females. Next slide.

So, Illinois began screening, as I mentioned before, in 2017. They used this different method with UPLC and tandem mass spec. The incubation is done separate for MPS II. So, there's an incubation -- again, I always hesitate when I have to talk about laboratory stuff being a non-laboratorian -- but there's a separate incubation stage, which takes a long time, and then the analysis is done by combining the -- the, you know, the stuff, you know, into the tandem mass spec machine. That was like the least scientific thing I think I've ever said in front of the Advisory Committee, so I apologize for that.

And GAG testing is not done by the -- by the newborn screening program. That happens afterwards. Next slide.

So, as I mentioned before, there's this separate punch and extraction time and the incubation period is seventeen hours. The analysis is multiplexed with other lysosomal storage disorders, and they have referral prior to GAG testing. The ScreenPlus is using

a similar approach, but I don't know what their incubations are or anything like that, and we're waiting for more information about how ScreenPlus is doing it. But they're using the same general method. Next slide, please.

So, by the end of May, they had nearly 560,000 specimens, of which 72 were positive, 23 which were due to pseudodeficiency, so 32 percent had pseudodeficiency -- leaving to 8.8 per 100,000 potential cases. Again, more to come and at our next presentation, we'll be able to really go through the numbers at different points in the algorithm. As with Missouri, no affected females have been identified. Next slide.

So, what I'd like to do now is just transition a little bit and talk about our process. So, in the review, we found in the initial search more than 4,000 articles and we're now going through those more in depth to see which ones are informative and we'll be forwarding to the review. We look at, as we always do, the natural history and epidemiology of MPS II, the analytic or clinical validity of screening. We look at the harms associated with screening for MPS II. We look at the benefits and harms for presymptomatic or early treatment compared to case detection.

In terms of better understanding this, we're also looking at why individuals or families might decide to stop ERT and also the degree of interest that the families might have in stem cell transplantation. And again, we're continuing to work with the TEP to make sure that we're asking the right questions and also to identify relevant gray literature, especially given that this is such an active area of research in terms of new therapeutics. Next slide, please.

So, I put this slide up to give a sense of the kinds of treatment outcomes that we look at. So, we always look at mortality and respiratory failure. I

put up a number of other outcomes that are traditionally looked at related to the condition and we will be outlining, you know, all these major ones and working with the TEP is relevant to identifying others.

This condition, when we move to the evaluation of the potential impact of a population we're screening, so we work with Dr. Costa and her colleagues too at the University of Michigan. It's clear that first of all, we're going to have to look at a time horizon if it's much longer so, you know, previously we could look at the impact of screening say two years after the newborn screening might have occurred. But a lot of the really important issues may take a lot longer to develop. And so from a -- we're thinking about that through right now in terms of the modeling and second technical expert panel, which will be held in mid-September is going to really focus on making sure we're thinking about the right outcomes and modeling things appropriately. Next slide, please.

So, you know, this is kind of obvious, but, you know, these are the things that we always do. So, you know, we're working on the evidence review, again the body of literature for MPS II seems substantially bigger than for some of the other conditions that we've looked at. We are working with our colleagues at APHL and Dr. Curtis on the Public Health System Impact Assessment and then I mentioned the work that Dr. Costa and her colleagues are doing around the population health impact of screening. In terms of the survey of newborn screening programs to assess their readiness and feasibility, right now we're also planning to have a webinar about that for states in mid-September. And then, you know, of course we're going to complete the cost assessment of, you know, for what it would be for the newborn screening program, focusing on the, you know, what the expected ranges of cost are. And again, it will be interesting given that there's two competing

methods for doing the screening to get a sense of whether or not there's a substantive difference between the two. Next slide, please.

So, at this point, I would like to open things up for questions, either clarifying anything that I've said or if there is any issue that the Advisory Committee really wants us to focus in on as we go about our work, that would be great.

CYNTHIA POWELL: Thank you, Dr. Kemper. We'll now open it up to questions and comments. First, we'll give Committee Members the opportunity to ask their questions or make comments, followed by organizational representatives. Again, please use the raise hand feature in Zoom when you would like to make comments or ask questions and when speaking, please remember to unmute yourself and state your first and last name each time you ask a question or provide comments to make sure that we can do proper recording in the minutes. Mei Baker.

MEI BAKER: Thank you, Alex, for the very comprehensive report. This is Mei Baker, Committee Member. I have a question. You mentioned that for the tandem mass assay, incubation time is seventeen hours. How about a microfluid method? What -- because the enzyme assay is only the incubation time?

ALEX KEMPER: So, my understanding is it's just on the order of a few hours.

MEI BAKER: Thank you. I did see that, but I wanted to verify it.

ALEX KEMPER: Yeah, again, we're going to be talking more with the -- the -- you know, the laboratory experts within the newborn screening programs to nail that down, and that's going to be important as we think about costs and other implications for the other newborn screening programs.

CYNTHIA POWELL: Any other Committee Members who would like to ask a question? Shawn McCandless.

SHAWN MCCANDLESS: Thanks, Alex. That's -- it's very impressive work so far, and I'm looking forward to seeing the final results. My question for you is for a progressive neurodegenerative disorder, especially with grey literature but even with the published literature, how do you account for sort of variability in the rate of progression and how does -- how do -- what's the method for -- for analyzing the data with that idea in mind?

ALEX KEMPER: Yeah, that's, you know, there's so many factors that go into neurodevelopment and as I pointed out too, I think some of the extra, you know, outside of the CNS involvement, you know, could clearly impact neurodevelopment as well and that actually came out very clear in its path. So, you know, if you're having trouble moving and, you know, I mean, that's how infants learn, right?

So, I -- I mean, there's no way that we're going to be able to like, you know, boil this down to a single metric. I think the best thing that we're going to be able to do is, you know, catalog what we've seen in terms of the impact.

You know, what's -- what does seem to be clear is that stem cell transplant doesn't have, you know, the effect that people were hoping that it would have. There are standard metrics that are used across studies in terms of looking at development. But I think at the end of the day that what we can do is just, you know, like we always do, catalog what we've learned. You know, this is a condition that affects on the order of, you know, what like a few, maybe, you know, through screening maybe 10 per 100,000, you know, and -- and neurodevelopment is so complicated.

So, what I hope to do, if we do our job correctly, is to be able to tell you the stories and then you're going to have to use your, you know, expert opinion and experience the way how much of that is due to early intervention versus not. That's probably not a very satisfying answer, but I think that's the best we can do.

SHAWN MCCANDLESS: It does -- I -- it came to mind when you were showing the photograph of -- the photographs of the two siblings who clearly had different physical appearance and different neurodevelopmental outcomes. But those neurodevelopmental outcomes were measured at different ages presumably and so the one with the higher neurodevelopment was also the younger and so it would be important to as much as possible try to compare people at the same age and those siblings at the same age would be very interesting data.

ALEX KEMPER: Yeah. Yeah, we can't, you know, I worry about having, you know, comparing an apple and orange. You know, we have to standardize things. One hundred percent, I agree.

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Hi, Alex. This is Melissa Parisi from NIH and I just had a question for you, which I think was triggered a little bit by Shawn's comment. I'm wondering if, at the time of your final evidence review, if you might have a chance to also give us an update on the current status of gene therapy efforts for this condition. I realize that requires a little bit of having a crystal ball and being able to see the future. But it would be informative, I think, to know what the -- what the current situation is for gene therapy for MPS II.

ALEX KEMPER: I one hundred percent agree with you and actually for the next presentation, what I plan to do is just like have a table with all the different studies that are going on and where things stand because I think that's an important piece of the puzzle.

MELISSA PARISI: Thank you.

CYNTHIA POWELL: Any other Committee Members who -- Jane DeLuca.

JANE DELUCA: Hi, Alex. Thank you for your presentation. No, I just wanted to clarify in terms of siblings that have the same genotype, the -- in your slide, you said the expectation is that the phenotypes will be similar. Is that -- is that the case or is it you'll have an uneven sort of presentation -- clinical presentation between siblings in the natural history without treatment?

ALEX KEMPER: Yeah, yeah. So, the technical expert panel -- and I actually sent a follow-up email to one of them about this just to clarify the point -- the expectation is that the -- the natural history sort of untreated phenotypes between the two siblings would be, you know, very similar. But, I mean, that's -- that's something we're going to have to dig up from the literature as well and I suspect an outcome survey can also provide us some insight into that.

So, I guess my answer is that the common wisdom is that they're the same, but we'll have to explore that in the data.

CYNTHIA POWELL: Any other Committee Members who wish to ask a question or make a comment? All right. We'll now open it up to organizational representatives. Dr. Berry.

GERARD BERRY: Oh, yes. Hi, this is -- this is Gerry from the SIMD. Thanks, Alex, for that wonderful comprehensive review. Could -- could you tell us a little bit about how -- how easy is it to distinguish between the less severe form and the early onset form in the post-newborn screening period and what impact do you think that might be for the families in being able to know whether it's one versus the other?

ALEX KEMPER: Yeah, you know, that's such a wonderful question that has like so many -- it's like an onion, right? There's like a million layers in that question because, you know, when you look at the -- well, let me back up and talk about my own progression in terms of thinking about this because when I first started reading the papers, I was like oh, this is going to be easy in terms of how they separate, but as it turns out, this is a very complicated spectrum disorder and I think that the terminology -- you know, as I had said before in terms of attenuated and severe and neuronopathic versus non-neuropathic -- I think it almost works against understanding the nuance of the condition and how profound the impact of the condition can be on families.

So, you know, it's obviously a severe disease and so, you know, my evolution in terms of reading the articles was like, oh, this was really easy to -- to put in the buckets. But now, you know, as you start to learn about something, right, everything becomes more complicated, now I think it's actually a lot harder to necessarily put subjects in the buckets. And then, in the world of newborn screening, right, what happens is therapy begins early. We are going to change, you know, the trajectory. I think that, you know, based on what I've read and have talked about with enzyme replacement therapy, you know, can have an important impact on the issues outside of the CNS, but it doesn't really seem to have the same impact as we would expect

on the CNS. But whether or not that's going to convert everyone who is severe into attenuated, I think that that's sort of a, you know, who knows -- who knows sort of. This -- let me -- let actually rephrase that. It's -- from what I've read and what I've seen, it's clear that the enzyme replacement therapy is going to have a major effect. It's -- it's not going to have the same effect though on the CNS system. So, it's not going to take somebody who is neuronopathic and make them non-neuronopathic and if you define severity -- severity as based on CNS disease, then those individuals might always be classified as severe. But from what I've read, even in the absence of making those changes and again from talking to people, I think it could have an important impact. Again, that will be for you all, you know, on the Advisory Committee to, you know, make that -- that final decision. But again, it's going to change, you know, newborn screening will clearly change the natural history. Did that answer your question?

GERARD BERRY: Yes, and speaking in generalities, I think we all realize that newborn screening is not a black and white affair and there's differences. I would imagine that if the benefit to the children of being detected early and then being put on therapy were -- were so significant that it would then outweigh the problems that maybe not being able to give the -- the correct -- the correct diagnosis in terms of severity, it would outweigh that. So, I guess that's some of the things we probably have to keep in mind.

ALEX KEMPER: Yeah, I think that's the issue and then again, it's the CNS stuff, right? So, you know, who is it that's going to need maybe some additional attention or therapy directed towards CNS stuff. I think that's -- even with newborn screening, that's still going to be an issue.

GERARD BERRY: Um-hum, yes.

CYNTHIA POWELL: Anyone else? Debra Freedenberg.

DEBRA FREEDENBERG: That's a great review. So, one of my question is if we detect this for newborn screening, is one of the outcomes we're going to be looking at is overall survival for those individuals detected by newborn screening or are we going to be quantifying them more in terms of our standard modifiers and what we're looking at for what we consider success for enzyme replacement therapy?

ALEX KEMPER: Yeah, you know, I think -- so, and it's funny and I should have mentioned this before. You know, probably half the cases are detected at birth that we've seen so far fall into the severe category and so, you know, we do know that those individuals have higher risk of earlier mortality. So, maybe we could, you know, see a difference there. Again, part of the problem though is just how long the evidence, you know, goes out and what we can model and what we can't. I think though that this -- this is, you know, again, this is an open question, so we're going to explore with the technical expert panel and, you know, what we can do with the data in terms of modeling. But I think that there are other patient-centered issues other than death that we could and should look at.

CYNTHIA POWELL: Any other questions or comments from our Committee Members or organizational representatives? All right. I had an opportunity to sit in on the first meeting with the technical expert panel that Alex and his group had, and it was very informative, and you've assembled a great group, Alex, and I certainly look forward to your update again at our November meeting.

ALEX KEMPER: Thank you very much. I -- I just want to say the technical expert panel was just unbelievably helpful -- really, really wonderful. We -- it was really, really super helpful. So, if they're listening, and I hope they are, I want them to recognize how much we appreciate what they did.

CYNTHIA POWELL: Thanks. Don't go anywhere, Alex.

Next on our agenda, Dr. Kemper will provide an overview of key issues identified through the Committee's review of the evidence review process, and I will discuss the proposed updates and next steps.

I want to thank the Committee Members, the members of the Ad-hoc Committee Processes Work Group, organizational representatives, and members of the public for their careful consideration and input over the past several meetings. I'd also like to thank Dr. K.K. Lam and Dr. Kemper for all of their efforts throughout the course of this project.

As I noted earlier today, we're close to finalizing the review and have identified updates that can be piloted immediately and others that can be implemented throughout 2022. I'd like to highlight that throughout this process, the Committee has explored some very complex questions, which will not be resolved at this time. We will go over this in the presentation, but some suggestions or actions will take additional research or policy changes and cannot be implemented at this time.

Dr. Kemper, I will now turn things back over to you.

OVERVIEW OF THE ADVISORY COMMITTEE'S REVIEW PROCESS AND PROPOSED UPDATES

ALEX KEMPER: Thank you very much, and I guess I -- first of all, I want to thank the Advisory

Committee for putting up with me during the second presentation. So, you know, it's a lot of listening to me. But we've done a lot of work and I just appreciate the opportunity to talk about it.

Dr. Lam, my partner in crime, has really worked extensively on the material that we're about to go through, and I really want to make sure that she gets due credit for things. Next slide, please.

So, way back in February of 2019, which is almost hard to remember given where the world is today, we convened an expert panel -- expert advisory panel to think through issues related to the whole process leading up to having something added to the Recommended Uniform Screening Panel or the RUSP. Next slide.

So, our objective is to inform the Committee about ways to strength then evidence review and decision-making process and also to develop consumer-friendly guidance to help with issues of transparency and really sort of understanding how the whole process works. Next slide, please.

So, a lot of these materials have been presented before. So, I'm going to go over it at a very high level, but, you know, please feel free to speak up or raise your little virtual hand if you want me to slow down and dig in on something more. But, you know, we -- we looked at everything from the nomination process to the evidence review process, the decision matrix, and then review of conditions that are already on the Recommended Uniform Screening Panel. One thing that I would remind the Advisory Committee is that that is not something that's -- that's routinely or regularly done. We have conditions that have been added to the RUSP based on specific questions that have been asked for us, but there's no, you know, standard process for doing that currently. Next slide.

So, the guiding questions on our work is thinking through, you know, what issues or changes are needed in the -- in the process, what are the next steps for doing that, how can we address those issues, and then also thinking about the timing of changing things, so what can be done immediately, what needs more work, and so forth. Next slide, please.

So, our approach, you know, as we do with everything, is convening expert panels, talking with members of the Advisory Committee, and in the interim summarizing things and talking about next steps including issues of actionability. As I alluded to before, HRSA and the Advisory Committee also convened another ad-hoc committee to go through what was in there, and now we're talking about next steps. Next slide, please.

So, this is to remind everyone of the long and winding road. I will not channel the Beatles and sing, so everyone can feel good about that. But the process that began back in February of 2019 leading to the presentation today. I'm not going to read through the slide, but I'll leave it here just for a minute just so that you can remind yourself of how we got to this point. Next slide, please.

So, what I'd like to do is to summarize key issues and then after I go through this, I'm going to hand things over to Dr. Powell, who can talk about what the Advisory Committee's perspective on things is. Next slide.

So, we revisited the nomination processes I talked about before and from that, we've worked on consumer-friendly guidance about how to -- how the nomination process works with material that will be posted to the Committee's website.

The next issue is information requested from the nomination form doesn't directly link to what we need in the evidence review process. And so, we have proposed revisions to the nominal form that will be forthcoming to the Committee website, as Dr. Powell mentioned, at the start of this meeting. This doesn't change anything for those individuals who are in the process of nominating a condition.

Again, the whole process was just to make sure that everything was in alignment to allow us to most expeditiously go through our nine-month process. Next slide.

One thing that we've talked about in the past is at the time of nomination, there should be some sort of review or landscape scan to identify what's out there, again, to sort of jump start and facilitate the evidence review process after discussing this and figuring out, you know, how could this be reasonably done without slowing down things. The plan was just to take no action on this idea at this point. Next slide, please.

Now, I'm going to switch gears and just talk about the review process. So, one thing that is critical when we do the review -- our reviews is that everything hinges on what the case definition is, what it is that we're trying to identify. The Advisory Committee can easily see how everything just kind of falls from there.

And so, in terms of the process of moving forward, we developed an approach to be much more clear about what the case definition should look like and what it should include and how the evidence review will work with the Advisory Committee to be clear about it.

The next thing was around figuring out what the important outcomes related to newborn screening should

be. You saw how this came up with the discussion around MPS II, and one of the things that we're going to be doing, and I think you saw that in the presentation, is just being very clear outright about what the critical outcomes are going to be from our review. In the future, one of the things that we might consider is using some more formal stakeholder process to rank the things that are most important. That's not something that's there now, but we in the evidence review side are going to be much more clear about the important outcomes as early as we can. Next slide, please.

The next was around assessing unpublished evidence -- the so-called grey literature. Given how fast many of the fields are moving and screening for treatment, it is important to look at the grey literature. What we have developed -- and we've talked about this before -- is a better method to be clear about the -- first of all, how we're going to find the evidence and to assess the quality of the evidence, and you'll hear us talk about that in subsequent meetings even around MPS II and similar to that, when we talked about this before, that on the evidence review side, given how tight our timelines are, certainly we're going to look to registry data and other important sources of data that have been analyzed in a way that we can use them. We, on the evidence review side, cannot do primary analysis of data, and that is, we can't take a dataset and just redo it ourselves. Instead, we're going to focus on the higher-quality grade literature that's already been analyzed. Next slide, please.

In the next part on the evidence review side, I just want to remind everyone we have the Public Health System Impact Assessment. And so, we have revised the survey that the states fill out, and when I saw we, I want to give APHL and Jelili a lot of credit for doing

that. That's in place. It's very hard to change that instrument because it has to go through the OMB paperwork reduction clearance, which can take eighteen months plus to get through. But I think we're in really good shape there and again, the revisions have been made to capture a better range of information.

The next thing was around cost estimates and how to make them more meaningful, and working with Dr. Scott at HRSA again, need to mention his name for MSP II review, we're going to be much more transparent about what those things cost and to provide really what's a reasonable range when we talk about what those costs are for the newborn screening program.

We have talked a lot with the Advisory Committee and others around other costs, like related to long-term follow-up plans, treatment, and that kind of thing, but that is an area that's very complex given the state of the availability and the evidence and the nine-month expectation for completing a review. That's not something that we can do right now, but it's still an open area of conversation because understanding issues of what systems are in place for long-term follow-up and how much long-term follow-up costs are important for planning to make sure that the individuals get the kind of care that we all want them to get. Next slide.

I'm now going to switch gears and a talk a little bit about the decision matrix and again, I don't want to rehash conversations that we've had before, but figuring out how to -- how to have -- interpret where we land on the decision matrix and the connection between that and the final recommendation can sometimes be confusing, especially when you're in the B rating world.

And so, we have developed additional guidance for how to think about things and talk about splitting

the matrix up from being this like multidimensional thing into a sort of separate two-step thing to help make those conversations more clear and more transparent.

But again, additional work is going to be needed around the relationship between the B ratings and how that ties to recommendations to the secretary, and again, Dr. Powell is going to talk about that in her section. Next slide, please.

So, right now, the decision matrix essentially ends up with a recommendation to the secretary that a condition should be added or that it shouldn't be added. But there's been a lot of discussion about whether there should be a provisional recommendation that is a very, you know, complicated issue in terms of what that means for newborn screening programs. And so, no action has been taken on that at this time. That's an ongoing conversation.

The next issue related to this is thinking about whether or not closely related conditions ought to be considered as a panel versus doing the one condition process at a time, which we're doing right now, and that's still an active area of discussion, and so, no action has been taken on that at this time. Next slide, please.

Values, we have discussed a lot, in terms of how do we assess the public perspective on the decisions that have been made. We've discussed this extensively at other meetings, and at this point, there's been no -- no action -- no particular decision has been made in terms of informing how the decision-making process or what will happen in evidence review has been made yet. And again, Dr. Powell is going to talk a little bit about that further. Next slide.

And then we have the issue of reconsideration of conditions on the Recommended Uniform Screening Panel. So, as everyone knows, once something is added to the Recommended Uniform Screening Panel, we learn a lot more about the epidemiology of the condition and the impact of early identification. There are a lot of challenges in terms of doing this related to, you know, where the data lives and the role of the reevaluation on conditions on the Recommended Uniform Screening Panel. So, this is still an area of active discussion. No particular action was taken about this at this time. Next slide.

And then, the next issue that we talked about a lot is developing priority in research and areas that need more development. Again, as we do our reviews, we often -- not often -- we always try to identify gaps in the literature. This particular issue is related to the Committee's role in terms of identifying research priority areas. We haven't taken -- and when I say we, it's really Dr. Powell and the Advisory Committee, has not taken a specific action on this at this time. But again, it's an important area for you all to consider. Next slide.

So, I am going to turn things over to Dr. Powell. But based on all the things that I went through in that very lightening fast presentation, there are issues that are either now actionable but need more discussion that you want to research or that needs some sort of policy change in order for the Advisory Committee to effect.

So, with that, I will hand things over to Dr. Powell, unless anybody has like a clarifying question or that kind of thing about anything that I went through in that blindingly fast presentation. Dr. Powell, I'll defer to you.

CYNTHIA POWELL: Yeah. We'll take just one or two if there's clarifying questions. Natasha.

NATASHA BONHOMME: Hi, Natasha Bonhomme of Genetic Alliance. When you were speaking about the evidence review and including families and parents and thinking of some different ways of doing that, was that focused on those families and parents who have children who are affected with that particular condition that would be under review and/or would there also be a process to get a more general perspective from, because though we talk about these conditions and the families that are impacted by them, we know that every newborn screening affects basically every family and every child in the country. So, just how are you -- what are you thinking around that?

ALEX KEMPER: Yeah. So, we -- such a great question and thank you for that -- that's actually one of the -- the conditions -- or one of the issues to be determined, and I think Dr. Powell is going to talk about that in her part. Still, we talked to some families right now just in terms of thinking about the outcomes that are important -- families who have children that are affected or affected individuals themselves, depending on the condition, to be able to prioritize the outcomes that are important. But the voice that we don't hear are the -- the families, you know, that are going to have children that would be tested through newborn screening but may or may not have the condition in the sort of general public, and that ties into the whole conversation we've had around values as well. And so, those are voices that are critically important that we don't typically hear right now.

CYNTHIA POWELL: All right. Thank you, Dr. Kemper. We'll next go through the various components of the process including, again, the nomination form

and process for nominating conditions, the evidence-based review, the decision matrix, and the review of conditions on the RUSP, and thinking about how we can proceed in terms of things that are actionable, areas that need more discussion, more research, and/or policy change. Next slide.

I'd like to say that there's a lot of information on these slides, and the slides will be available on the Committee website following this meeting. And in green, are areas of suggested actions or changes. So, first we'll talk about the nomination process.

As noted in Fiscal Year 22, we will have consumer-friendly guidance and frequently ask questions on the nomination process available. The revision of the nomination form will be adopted in Fiscal Year 22. And again, if you look at the current nomination form, most of the recommended changes are not, you know, major changes. It's more clarification of, you know, what's being asked. And I think, you know, it seems to me that that's helpful so that those who are nominating conditions aren't thinking, you know, what is the Committee asking for here. So, it provides more clarity to what's being asked. There are a few additional questions that are being suggested for addition to the form.

So, again, information about the condition including the enzyme, including the specific case definition for the screening target, include the US incidence, the estimation, and citations for that, and what is the timing of clinical onset for phenotypes that would be detected through newborn screening for the condition. What's known about the severity of disease, the US distribution, the prevalence, and describe the medical and clinical care required?

Identify which treatments are current -- the current standard of care for the condition. Next slide.

Continuing with the condition information and treatment, what's the clinical indication for treatment as well as the urgency? What are, again, the current standards of care, and are there contraindications for treatment initiation?

On terms of the efficacy or benefits of newborn screening, again, what are the known phenotypes that will be detected? And then, what's the availability of treatment and follow-up? Are these available in most hospitals? Would primary care providers be able to do this? Would they only be available in major medical centers and descriptions of the follow-up and what would be needed in those specialized treatment centers will be helpful. Next slide.

In terms of the evidenced-based information, what is the modality of the screening specimen samples, descriptions of the screening test, the platform, and procedures? What is available information regarding high-volume screening methods, instrumentation? Would screening be available as part of a multi-analyte platform? Are these lab-based analyses or off-the-shelf kits? Are they FDA approved? And then does the screening algorithm include a second-tier test? What would be the modality of that specimen sample for a tier-2 test? Would it be done off of the same dried blood spot? Would additional samples, various types of samples -- urine or other -- be required?

And what has been done regarding the clinical validation -- the number of samples that has been run through high-throughput screening methods? And in terms of analytical validation, has the CDC newborn screening and molecular biology branch been contacted regarding validation measures?

In terms of the diagnostic testing and timeliness, is this a critical condition or is, you know, one of the forms of the condition that would be detected through newborn screening critical in terms of timeliness? What's known about that?

And then for the confirmatory testing methods, what types of samples or specimens are needed? And again, what's known about the clinical and analytical validity of those confirmatory testing methods? Is it quantitative or qualitative? What's the sensitivity and specificity? Next slide.

In terms of the confirmatory testing again, is there FDA approval of those confirmatory testing methods? What's the availability of confirmatory testing? Would samples need to be sent to specialized testing centers in order to determine whether a case would be a true positive or not?

And then in terms of prospective pilots, have there been US and/or international pilot studies done? If in the US, to cite the cities or regions of the screening method and algorithm that was used in the pilot and describe the screening method, provide a flow chart with pilot outcomes in terms of how many infants were screened, how many positive and negative screens were there, how many of those were ultimately determined to be true positives versus false positives, and what confirmatory testing methods were done, in what order were they done, and as much information as possible about that.

Were the numbers of infants confirmed with the diagnosis in pilots and what was the outcome? What were the number of infants with positive screens versus those who were actually diagnosed? And again, information regarding the timeliness. Evidence about outcomes, when possible, the duration of the follow-up

period and describe plans for longer-term follow-up of newborns detected early.

Providing contacts for the pilot studies that may have been done and then information about states that are considering screening for the conditions or states that are currently screening, or those that may have state mandates that would require screening within a certain period of time.

Again, something we've talked about a lot, but patient registries or databases and the contact information for those databases. And then including unpublished data that would inform newborn screening. Next slide.

In terms of the -- going on now to the evidenced-based review process, Dr. Kemper has already covered these, but in terms of those that are now ready for implementation, assessing published evidence, clarifying the case definition, and specifying priority outcomes, identify those available and not available in evidence.

Assessing unpublished evidence that's ready for implementation. Formalizing current procedures and framework for inclusion and continuing to consider registry or unpublished data evidence, applying formal assessment framework.

And for the Public Health System Impact, the PHSI Survey has been revised. That's been done and it's ready to implement with, for example, with the MPS II review. A new Disorder Readiness Tool has been developed and cost estimates in broad categories rather than point estimates will be adopted in Fiscal Year 22. Next slide.

With the decision-making process and the matrix, additional guidance regarding that, more information regarding the decision matrix purpose, how

to use it in deliberations, considering each criterion individually and how to incorporate into the matrix rating.

Additional guidance has been drafted regarding describing each criterion and individual matrix ratings, high versus moderate versus low certainty of evidence, for example. And the Committee received in their briefing book the draft of the final report and also information regarding specifically the decision matrix. I think breaking it down into the individual parts is really helpful in terms of how the Committee Members can just improve the thought process when deliberating a condition. Next slide.

In terms of establishing a plan to conduct the regular review of conditions on the RUSP, as Dr. Kemper mentioned, this is something that the Committee has not done in the past. But it was felt by Committee Members and others that it would be helpful to do this, but we would need to decide how often to do it. Would there be a method of prioritizing which conditions to review first? Would conditions to review be nominate or how would they be selected? What would be the considerations and criteria, and what would be the goals and outcomes? And this will be discussed further next fiscal year.

In terms of assessing long-term follow-up of newborn screening, again we will continue to discuss this issue further. What is the impact of newborn screening? How can we get a better grasp of this? As you know, that's an area that I've been, you know, very interested in. I think it's really critical for what the Committee is, you know, being asked to do. We really have very little in terms of available data in short- and long-term follow-up, especially across the US. Where there are certain states that are doing

this, the majority of states are not, often due to lack of funding to do this.

And so, we think about the costs of implementing this, also looking at what are the costs of treatment for the conditions that are on the RUSP, and what's the impact on health care system and providers? Have there been sufficient places where infants identified through newborn screening have been able to go and obtain appropriate both short- and long-term follow-up care? And what has been, you know, has that access been equitable? How difficult is it to access care, and not only in, you know, major metropolitan areas, but in more rural states? Next slide.

So, we hope to establish a priority list of research and development issues. That work will be ongoing. As I said, we'll revisit the decision matrix further. We'll also continue to discuss long-term follow-up in newborn screening, and then an area that a number of past and current Committee Members have brought up is how to assess the values of stakeholders and a thought that, you know, we haven't been able to include all stakeholders in terms of, you know, getting feedback when new conditions are being considered and how do we go about doing that? How do we include them in the decision-making process? Again, that's an area of further discussion. I think, you know, we talked a bit about particularly families, the public, not only those who have had children with conditions identified or potentially identifiable through newborn screening, but also families who may have experienced going through the process when it's ended up being a false positive result and just general feedback from the public. What are values and preferences for some of the critical outcomes? Next slide.

So, again, the major issues. Communication regarding the purpose of the decision matrix is lacking. It's a complex tool. Again, actionability, confirming the process of using the decision matrix for the Committee to determine recommendations and actions within the decision matrix and in some of the past or most recent decisions that the Committee has made in terms of the B ratings where there's, you know, there's a moderate certainty of evidence. Guidance is scant about this. There's been some, I think, concerns about the B ratings that some successful nominations have had. It's not entirely clear about, you know, the B rating. So, additional description of the B rating can be developed using past reviews that have had a B rating and perhaps creating a tracker or score card.

In terms of net benefit, it's also a bit unclear regarding what should be considered and the net benefit regarding the sum total of benefits versus harms and descriptions for each criterion within the decision matrix are limited for the complexity of conditions. So, additional guidance was included in the final report regarding, you know, these considerations and how to better define some of the components of the decision matrix. So, that's been done. It's still in draft form, but it has been completed.

And then going forward, to consider further transparency efforts by requiring scoring or rating of each matrix criterion and then an overall rating that's collected with the vote, comparing it, for example, to the NIH grant review scoring and the EVIDEM scoring rubric. Next slide.

In terms of long-term follow-up information, plans or screening outcomes or costs. The meeting attendees underscore the importance of describing long-term follow-up plans for conditions nominated for

addition to the RUSP. This includes the diagnostic testing, treatment, and possible longitudinal surveillance. Again, for further discussion, further research, and possible policy change.

And conducting follow-on or follow-up assessments of screening outcomes, costs, treatment access, and follow-up reviews of RUSP conditions. The meeting attendees further underscore the importance of continuing to assess the cost implications and outcomes after a condition is added. This information could help state public health programs prioritize and budget new screening programs and provide feedback regarding the Committee's activities with newborn screening and also help inform whether treatment access maintains equity of newborn screening or if gaps and issues need to be addressed. And again, there will be further discussion of this as we go forward, further research, and possible policy change. Next slide.

So, again, the key issues identified by removed from consideration for feasibility is a scoping review during the Nomination and Prioritization Work Group Review to address the nomination package bias. Currently, there is limitation to how much of an in-depth review can be done by that work group, but that is an area that perhaps given additional resources in the future, we may be able to do.

Expansion of the decision matrix to include conditional or provisional recommendations. Not to say that that isn't important to consider, but it was felt that at this point, it just wasn't feasible to proceed with.

And then, how do we consider multiple conditions concurrently and that's certainly something that we'll need to continue thinking about in the future. But it was not felt to be something that could be enacted immediately or in the near future, but

consideration of more -- more thought and work in the future.

And I think that's my last slide, yeah. So, now, we will open it up to first questions and comments from the Committee Members, followed by organizational representatives. As a reminder, please use the raise hand feature in Zoom when you would like to make comments or ask questions and when speaking, please provide your -- unmute yourself and provide your first and last name each time you ask a question or provide comments to ensure proper recording.

As we begin the discussion, please remember the plan is for the Committee to hold a vote on whether or not to approve the updates at the November 2021 meeting, so our next Committee meeting.

All right. Any Committee Members who would like to comment? Scott Shone.

SCOTT SHONE: This is Scott Shone, Committee Member. So, I'm struggling with what and how to say my thoughts on the presentations. So, I appreciate -- let me start by saying I appreciate all of the work that's gone into it. I'm kind of disappointed because I feel like we missed the mark on some really significant issues that precipitated the need for this discussion review, and I think that some of the things that have been put off have been put off a lot by our group because they are difficult and they are challenging to talk about and think about. You know, I'm a laboratorian by training, and I've learned a lot from my follow-up colleagues over the years, and I appreciate all they have said and done to teach me. I think the long-term follow-up piece of this that keeps getting pushed off is very frustrating. I think we've well established a need for it. I think we've well established that that is the data that drives our ability to make data-driven decisions on where we go

with newborn screening. And it's frustrating, I think, the fact that it gets put off meeting after meeting of it's big, it's resource-driven, et cetera and as a state lab director, having seen the volumes of money that are flowing in the pandemic, to think about what could we do if we had a fraction of the dollars coming into infectious diseases for this community and what we could -- how we could change the health of newborns and children is what this Committee is all about.

So, I think that I would encourage us to think about long-term follow-up with more discrete and time-driven actions moving forward so that we can really think about how to facilitate -- learn lessons from the states that are doing it and it well and facilitate implanting that across the country. So, that's my first thought and that's long-term follow-up.

I think we've well established that there's inequity across the country intermittent terms of access to care. There were a couple comments in the slides around looking more at what are the challenges in rural communities and this and that, and I think we've heard time and time again from our wonderful advocates who get up at public comment and talk about the deserts of care and we know a lot about that, and I think we just need to take that data and -- and try to be -- try to be forceful about it, and I would ask Dr. Warren if there's an opportunity to leverage the Office of Health Equity in HRSA to have a cross-agency collaboration to look at how can we think broader than just the Advisory Committee of Heritable Disorders in Children and the Maternal and Child Health Bureau to try to solve some of these issues because we do know that these exist and we've talking -- again, we've talked about them a lot, and I would love to be part of actions to drive ways to think about that.

And I'll end by just saying, you know, I think the nomination process still drives a lot of advocacy groups and scientists towards newborn screening of dried blood spots, and I think we pigeon-hole groups into that, which creates a burden on the newborn screening system itself and dried blood spots, looking for biomarkers that are solely in dried blood spots and then burdening -- I'm going to talk about workforce issues tomorrow and further burdening the system that way. And I think, you know, I'm occasionally -- and I'm thinking about what if we had a nomination package for, you know, urine in a 6-month-old that could 100 percent -- with 100 percent sensitivity identify a certain disorder. What would we do with that? And we are the Committee on Heritable Disorders in Newborns and Children. I think that there might be opportunities that we're missing to really think about ways we can impact children's health and look for disorders that have therapeutics beyond the massive overwhelming number of genetic therapies that are coming for all these other disorders.

So, I think there -- I see -- I understand the plans for FY22, but I think we need to think with more action and -- and the time has -- has almost passed based on the topics we continue to talk about. And I'm happy to put my actions where my mouth is and participate on any group that I've just tagged as needing to be part of a longer-term solution get things done. Thank you.

CYNTHIA POWELL: Thank you. Dr. Kemper or Dr. Warren, did you want to have an opportunity to address?

ALEX KEMPER: Well, I mean, I'll defer back to you in terms of the -- the -- you know, what the Committee does moving forward. On our side, we're happy to do whatever, you know, it is that we're

charged to do. So, I'll defer that to you and Dr. Warren.

CYNTHIA POWELL: Dr. Warren, you're muted.

MICHAEL WARREN: Thank you. Sorry, guys. Thank you both, Dr. Kemper and Dr. Shone. I, certainly on the equity issue, would be happy to explore that both with HRSA's Office of Health Equity and the broader equity work we're doing in the Bureau -- the strategic plan we just released. Equity is one of the four key goals. So, this aligns very well with where we're at and would welcome additional conversation there.

CYNTHIA POWELL: Any other -- Annamarie.

ANNAMARIE SAARINEN: Hi. I'm Annamarie Saarinen, Committee Member. Thanks for all this great work and I've been glad to be part of the last six or eight months anyway of the subcommittee working on this. And Dr. Shone, I really appreciated your thoughtful responses there. I was nodding my head with pretty much everything you were saying.

I did have a little -- a couple of procedural questions, if that's okay. And one -- and forgive me if I missed it as a lead in to the presentation. What will be happening between now and the proposed November vote? Is there any expectation that there would be an opportunity for modifications, updates, feedback, things that might change in either a small or substantive way as this is put before a Committee for vote in November? That's procedural question one.

Procedural question two ties to, I think previous meetings and consensus around what sounded like from your both -- both Dr. Powell and Dr. Kemper, from your reports, it sounded like kind of concrete decisions or concrete recommendations have been made by the work group around -- sorry about that guys --

around long-term follow-up, around provisional review, and potentially provisional acceptance if the framework or guard rails were there and there was a third one too that I was thinking about -- oh, multi-condition review -- multi-condition review because I remember us talking about it and working through some sort of pros and cons, but it felt a little more concrete in this presentation than I remember it being in our last meetings. So, those are just my comments, and again, really appreciate this work and I -- I feel that sense of urgency of making some of these things actionable versus like we've been talking about them for a really long time, and I understand there's work that goes into this and I to the degree I'm able would be willing to step up in any way that can be useful. But I think those three subjects in particular play directly -- directly into health equity for the babies and children that this Committee and all of the state programs are aimed to serve.

CYNTHIA POWELL: So, in addressing your -- your first question, you know, the slides will be posted. There will be more opportunities for public comment. Committee Members will, you know, have opportunities to review the more specific changes. Certainly, there will be, you know, another presentation and opportunity for discussion as well as, you know, suggested additions and changes at the November meeting. So, I think, you know, nothing is set in stone at this point and, you know, thinking about some of the, you know, the other areas, you know, hopefully it -- while we may not be able to vote on them in November, you know, I think that if it's something that the Committee feels strongly about that, you know, it shouldn't be postponed. These things do need to move forward. That, you know, we'll be able to address those -- those things. I mean, I totally agree with, you know, your concerns and Scott's concerns, you know, that, you

know, multi-condition review, you know, is something we need to think about as well as the long-term follow-up. So, I think, you know, areas where it's felt that additional data is needed or possibly research, you know, that is something that we have to look to HRSA and, you know, what are their funding abilities at this time.

So, Alex, I didn't know if you wanted to make any comments.

ALEX KEMPER: No, I don't really, you know, again, on our side, we're happy to do, you know, whatever we're charged with. So, I don't want to stretch into anything related to final decisions.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Thank you. This is Shawn McCandless, Committee Member. Being newer to the Committee, I -- I don't -- I wasn't around, I think, when this activity started in the -- the pre-COVID era. So, the questions that I have that are not clear to me is what is the actual goal or driving need behind this review? What are we trying to accomplish with this review in this action and specifically, is the goal to improve equity for conditions that are being added to or for the patients that have those conditions? Is it to enhance the speed or the ability to make these decisions? Is the goal to enhance transparency or the standardized evidence review to further standardize the evidence or are there other goals? It just would be helpful to me to understand what was driving this in the first place.

ALEX KEMPER: Yeah. Let me just take a quick stab at this and then hand things over to Dr. Powell. So, you know, we've been doing these evidence reviews for quite a while and began to learn lessons around what worked and what didn't work and what would improve

our efficiency and then also, critically important, what would improve transparency. And that's what led to a series of meetings, really looking at the entire process from, you know, I think about it as how a bill becomes a law, right? So, like how things become nominated to when the final vote was made and as we began to look all components, it just became more and more complex when we decided to look at each little bit.

So, certainly, you know, we very much want to promote equity but, you know, there's everything else around making sure that the Advisory Committee, you know, is best able to make a recommendation on transparency with the public, you know, and all these other things that you mentioned.

And so, what happened is it quickly grew into a very complex and comprehensive series of projects. But in terms of, you know, where that's going to go and those kinds of things, I'm going to get things back over to Dr. Powell because I don't want to pass what we do in terms of evidence review.

CYNTHIA POWELL: And I didn't see Mia's hand up before, but Mia, did you want to comment?

MIA MORRISON: Yes. Thank you, Dr. Powell. And I think at this point, I just want to say I know that the conversation is continuing and I want to thank the Committee Members that provided their feedback throughout this entire process and also today. And I want to mention that the vote that will occur in November by no means is meant to end conversations that very much should be ongoing. We need to start to implement and to put into action some of the changes that can strengthen the process immediately, but I want to emphasize that it won't mean that further discussion is ended, and I want to thank Dr. Shone for pointing out, you know, that he's willing to help participate in

further conversations and work groups because I think that it's important that as a Committee we don't kind of stop at the end -- at the end of this vote, that we continue to look for ways to strengthen processes moving forward. Thank you.

CYNTHIA POWELL: And Shawn, just to, you know, address your question in addition to what Alex said, I -- I think, you know, it wasn't just one thing, it was sort of a global feeling that, you know, when the decision matrix was first implemented, you know, we weren't sure exactly how it was going to work. Would it be successful? I think there were some issues as it went on and as the, you know, specific conditions were reviewed utilizing the decision matrix and voted on using the decision matrix, that it was felt that, you know, it's always good to review the process and how the Committee is going about making decisions and, you know, again some feeling that not all parties were being heard from, when there would be votes, as well as, you know, other things like the nomination form that, you know, it was thought to be deceptively simple that, you know, it looked on paper that it was really easily to fill out and that wasn't always the case and what really would, you know, help the evidence review process, you know, required additional information. It would be very helpful to get that additional information. So, things like that.

So, let's see. Annamarie, did you have another comment or did you still have your hand up from before?

ANNAMARIE SAARINEN: Yeah. Sorry about that, lowering now.

CYNTHIA POWELL: Okay, no problem. Any other Committee Members now with -- if not, we'll go ahead to the organizational representatives and Chris Kus.

CHRISTOPHER KUS: Yes. Scott, I really appreciate your comments, and I wonder whether you could briefly summarize your suggestions in writing so I can consider them seriously. I'd appreciate that, thanks.

CYNTHIA POWELL: He's giving a thumbs up for that. Robert Ostrander.

ROBERT OSTRANDER: Robert Ostrander, liaison from American Academy of Family Physicians. I also appreciated your comments, Scott, and specifically as, you know, part of the Follow-up and Treatment Work Group, I would suggest that what was sort of drawn out in broad terms in today's presentation be sort of a formal narrow requirement that at least an architectural blueprint for follow-up and treatment both what's available to accomplish it and what's available to measure it be a requirement of the nomination process.

My main ask here is consideration and perhaps some comments from Alex about whether the non-disease specific treatments that could be implemented and have benefit in terms of the course of illness, prolonged ambulation, those kinds of things could benefit from early diagnosis, preclinical diagnosis are ever considered because it seems like all we talk about is the disease-specific treatments. But having, you know, done some work on the DMD issue aside from the disease-specific treatments, you know, there's a pretty strong feeling that by having this diagnosed early, even preclinically, and getting kids enrolled that providing these non-disease specific treatments modifies their course.

Now, it may not be feasible to consider this. But just because something isn't pharmaceutical doesn't mean it's not beneficial and it doesn't mean it's not

useful when applied earlier than it would be if you had to wait for clinical diagnosis.

ALEX KEMPER: That's a great question. We do actually look for any evidence regarding the benefit of early identification versus later identification regardless of whatever, you know, additional supports are given. It just happens to be that the cases -- the conditions that we've at before have had, you know, like specific, you know, drugs that can be given. You know, you can imagine maybe there might be also a condition where there would be some pharmaceutical intervention that wouldn't be given until, you know, some period of time later or whatever. But we would think about that and also think about the non-disease specific supports that individuals might get.

So, I mean, that's a long-winded way to say oh yeah, we would definitely look at that. It's just that the conditions we've looked at have all had the kinds of interventions that would begin as soon as diagnosis was made.

Certainly, you know, DMD brings up all sorts of, you know, potential supports that those individuals would get as well as, you know, steroid therapy and that kind of thing. But regardless, we would look at whatever we could find regarding the benefits and harms of early identification versus when it might come about through usual clinical identification. Does that make sense? Okay.

CYNTHIA POWELL: Natasha Bonhomme.

NATASHA BONHOMME: Hi, Natasha Bonhomme. Thank you to everyone who already spoke and all of the comments from the members and the org reps. I think it's really shown the different conversations that we can and should be having in the upcoming years. I have a question and a comment.

My question is, when talking about the consumer-friendly materials, has it been discussed exactly like how that would be tested or what would be the markers of success for that or is that, you know, to come later down in the process?

And then the comment is, you know, seeing that we have had a bit of this discussion around equity, seeing that in terms of the discussion around long-term follow-up, it's just kind of a reminder to know we know just how equity is an issue throughout the entire health care system. It's also an issue throughout the newborn screening system, not just the long-term follow-up one. And just thinking again whether it's just in this iteration or future iterations and phases as Mia was speaking, to really think about, you know, how is the nomination process an equitable one and how can we make it even more so in testing that out and seeing, you know, whether it's reaching out to people in groups who started the process and stopped and understanding what were those issues. I'm just saying even from a logistical perspective, there are some equity considerations that would be good to look at. Thanks.

CYNTHIA POWELL: Thank you. And I think Shawn McCandless will be addressing some of the things about equity that you mentioned.

ALEX KEMPER: I can respond to that about the consumer-friendly stuff. So, you know, it sort of hits at two different levels. One is the good news is, you know, we have someone that can help us write at the appropriate reading level, but that's not the same as having something that's -- that's accessible and understandable and hits the mark. So, that's certainly ongoing work and I'm happy to talk to you offline about the best way to do that. I mean, clearly, you have

deep understanding of how to go about doing that. So, it's -- it's still a work in progress.

NATASHA BONHOMME: Great. Thanks, that's helpful because yeah, consumer-friendly is not just a seventh-grade reading level. It's a lot especially with something as complex as this. So, that's great.

ALEX KEMPER: One hundred percent agree.

NATASHA BONHOMME: I'm happy to talk to you, Alex.

ALEX KEMPER: Hundred percent agree.

CYNTHIA POWELL: And hopefully those will be updated on a regular basis based on feedback that we get from groups. Also, one of the good things about FAQs, you can always add additional questions on that are coming up frequently.

Any other questions or comments from anyone who we haven't hear from? All right. Well, clearly these are areas of much interest and importance. As we move forward, it's my hope that we'll be able to address all of these things, even those that may not have risen up to the very top at this point. But hopefully there will be available funding and resources to implement many of these things.

I think -- let's see -- we're almost on time. We're a little bit early for our public comment period. Mia, is it okay to proceed with that now?

MIA MORRISON: Yes. Please, go ahead.

PUBLIC COMMENT

CYNTHIA POWELL: So, we received one written public comment and nine requests by individuals to provide oral public comments to the Committee today. Committee Members received a copy of the written comment prior to the meeting. At the May 2021 Advisory

Committee Meeting, we had two public comment periods. One was open to any newborn screening-related topic and the other was specifically dedicated to the Committee's review of its nomination, evidence review, and decision-making processes. We received important feedback from stakeholders and wanted to provide another opportunity for the public to submit comments on this topic for the August meeting. The following questions were posted to the Committee's website. Is there a next slide? Maybe not, okay.

On the condition nomination form, what additional information would better inform the Committee such as proposed case definition and screening target, long-term follow-up outcomes, list of known registries, and unpublished data contacts? What information is difficult to obtain? What types of data and/or information should be included in the evidence-based review to better inform the Committee? Next slide.

The decision matrix is a tool to assist the Committee in making decisions. Are there suggestions for additions or edits on the decision matrix?

What types of educational materials would help to explain and clarify the Committee's condition nomination, evidence review, and decision-making processes? And any other comments or input?

We received two requests to provide oral public comment in response specifically to these questions. Mr. Dean Suhr and Ms. Elisa Seeger will deliver those remarks in a few minutes. Committee Members also received a written version of Ms. Seeger's statement.

As I mentioned earlier, members of the public have noted issues that the Committee will not be able to address in the current set of proposed updates. However, this doesn't mean that the conversation ends

here. Feedback that cannot be addressed at this time will be kept under consideration as we move forward.

We will now hear from those individuals who registered to deliver comments today. The first six individuals will address the nomination of GAMT Deficiency to the RUSP.

First up, we have Kim Tuminello followed by Heidi Wallis in terms of order. Then we'll hear from Dr. Longo and Dr. Pasquali, and then Becky and Stu Tribe.

KIM TUMINELLO: Okay. Can you all hear me?

CYNTHIA POWELL: Yes.

KIM TUMINELLO: Great. Thank you. Good morning. Thank you for having us today. My name is Kim Tuminello, and I'm a cofounder for the Association for Creatinine Deficiencies and currently serving as Director of Advocacy. However, my most important role is that of being a mother of two children who were both diagnosed with GAMT, the condition which you'll be voting on later today.

For those of you who may not be familiar with this rare disease, we were here in 2016 when GAMT was first nominated for the RUSP. I think there are probably many of you here today that watched the rather long and difficult debate on whether to vote GAMT to the Evidence Review Board. Obviously, at that time, it did not move forward, but not because it wasn't a serious medical condition or had an incredibly safe and effective treatment that is inexpensive and easy to detect, but because at least one baby had not been positively identified during a newborn screen. That was the only criteria that had not been met. The heartbreak in the room was palpable and not only by me and the other mothers, but by several of the Committee Members who had voted to move it forward. As a mom,

knowing the difference of a child that not detected until he was 10 months old and a younger sibling that was treated from birth, I knew what devastating consequences there would be for children and families to come and yes, there are babies in our community today that would have benefited.

After that vote in 2016, Dr. Bocchini kindly approached our group of moms and told us not to give up, that this would probably eventually be put on the RUSP but that we need to advocate in other states and to come back as soon as that baby was found. Today, we are here again because that baby was found in Utah and then another shortly after in New York.

I'd also like to briefly mention the cost of testing for GAMT is estimated to be as low as 30 cents per baby. But a study done by CHOPP says a child with an intellectual disability or autism spectrum disorder is costing today around $2.4 million. We simply cannot afford to not test for GAMT. But here is the reality. My son who was diagnosed at 10 months old is now 15 years old. He has seizures, speech problems, feeding problems, tactile issues that affect his everyday life, fine motor skill impairment like brushing his teeth and shaving himself, and social and learning difficulties. However, my daughter is a typical kid in every way, is a great student, and requires no school assistance, IEPs, or therapy of any kind, and will never be a burden to the state in any way. She just joined the water polo team, plays soccer, and has a thriving social life. I see the differences every day -- every heartbreaking day.

We know that you have a tremendous responsibility here today and we are thankful to be here with all of you. We believe that GAMT is and always has been the perfect disease for newborn screening. Please move it forward today. Thank you.

CYNTHIA POWELL: Thank you. Before we move on to our next comment, we do not have Becky and Stu Tribe on. If you're present, can you please raise your hand so we can identify you and make sure that your mics are open for your presentation.

All right. We'll next hear from Heidi Wallis.

HEIDI WALLIS: Good morning or afternoon. Can you hear me?

CYNTHIA POWELL: Yes.

HEIDI WALLIS: Okay. Great, thank you. My name is Heidi Wallis. I am the parent of two children with GAMT Deficiency. I'm also the President of the Association for Creatinine Deficiencies, and I additional work in the Utah Public Health Lab in the Newborn Screening Program.

Today, I'm here with high hopes following the good news of the two babies who have been identified with GAMT through newborn screening, as Kim mentioned. In 2016, GAMT was not moved forward to evidence review by one vote based on the newly introduced criteria requiring a prospective identification of a baby with GAMT through newborn screening. This criteria has now been met twice. I would like to think that GAMT has no barriers at this point, but I will try to reassure you with a few points that this is indeed the no-brainer disorder for newborn screening, as it has so often been called.

Point number one is GAMT is serious. As Kim mentioned, there is a neurotoxin that builds up in the brain of children with GAMT. This begins shortly after birth and children like my daughter, Samantha, who is 18, are born looking typical. They are not identified as having any problems and seem unaffected until the damage has been done and there is long-term effects. And based on my experience with families, if the

diagnosis is not made within the first few months of life, the effects are not repairable.

Number two, GAMT cannot be easily detected. We can't rely on pediatricians for a timely diagnosis. Diagnosis of GAMT before GUAC impacts the brain can only be accomplished through newborn screening or family history. There is no telltale dysmorphic feature that we can rely on or even a common manifestation of symptoms over time. Doctors struggled to diagnose my daughter. She was diagnosed with global developmental delay, then autism spectrum disorder, until finally at 5 years of age -- 5 years of having that neurotoxin on her brain -- she began to have seizures and she has not recovered from those seizures. She still has seizures and they are progressing.

Number three, treatment works and it costs less than a newborn's diapers. It's incredibly affordable. It's over the counter and safe. My 9-year-old son, Louie, who was diagnosed at birth because of his big sister, is unaffected by GAMT today. Because of this, I know my daughter's life could have been changed had she received treatment at birth like her brother. She wouldn't have seizures or be intellectually disabled, but that can change starting now for families with this Committee. Individuals of GAMT can live normal, healthy lives if treatment can start shortly after birth.

So, finally with all of this seeming like we've checked all the boxes, I want to address some points that shouldn't matter, but they have been raised by some people, and I don't want these to affect anyone's opinion.

Number one is the perception that GAMT is just too rare to screen for. While the true incidence of rate of GAMT won't be known until there is more screening, but there are estimates as high as 1 in

120,000. Arginase deficiency, a RUSP condition, has an estimated instance of 1 in 300,000. How rare a disease is or is not should not matter. But GAMT isn't the rarest of the diseases on the RUSP.

Number two, GAMT is too hard to screen for or as one Committee Member commented to me off record, it would be so much easier if GAMT were in the Perkin Elmer kit. Well, GAMT is not hard to screen for. As the recently published paper, Prospective Identification by Neonatal Screening of Patients with Guanidinoacetate Methyltransferase Deficiency details, GAMT patients have levels of GUAC well above the cutoffs set by New York and Utah. They are easily identified. The screening for GAMT is accomplished by adding the analytes GUAC and creatine to the already performed mass spec testing of amino acids and acylcarnitine. Perkin Elmer is currently working to integrate GAMT marker measurement in their non-derivatize -- excuse me -- nonderivatized MS/MS assay. More data will be presented by Perkin Elmer in the APHL Newborn Screening Virtual Symposium.

Finally, number three. It's expensive for states to add GAMT. As I just mentioned, this is one of the least expensive RUSP additions proposed. It requires no additional blood spot, no additional instrument, or additional staff. It's two extra analytes from a test already being performed. States cannot afford to not screen for GAMT when considering the cost to society of an intellectually disabled citizen.

I ask that you consider the facts I've shared along with your sense of what is right for GAMT families across the US and vote to move GAMT forward to the Evidence Review Committee. Thank you for your time and your consideration.

CYNTHIA POWELL: Thank you. Next, we'll hear from Dr. Longo.

NICOLA LONGO: Thank you very much for giving me the opportunity to talk on this panel. I'm a medical and biochemical geneticist as the University of Utah and I treat children with intellectual disability and metabolic disorder.

What strikes me about GAMT Deficiency is the similarity between this condition and Phenylketonuria, the very first condition included in newborn screening. Children are perfectly normal at birth and then they fail to obtain milestones as they grow older and then many of them become hypertonic, most of them will develop seizures and movement disorders, and many of them are diagnosed with autism. So, the presentation is totally nonspecific, and that is why the diagnosis is usually not reached until it is too late.

The therapy consists of administration of creatine that blocks the reaction of mild or moderate protein restriction, and many times we give sodium benzoin. All of this therapy can be found on the internet. Most of the parents find them on websites and obviously they are relatively inexpensive and easy to obtain in addition of being pretty safe.

Now, a few children, I have heard, have been treated since birth based on family history, and they have done very well. And the same thing seems to be happening to the two children identified by newborn screening, keeping in mind that one of the two children had an older sister who had GAMT Deficiency that had not been diagnosed but was diagnosed after this child was born, and she was started on therapy. The older sister was already showing symptoms at a few months of age. This child is perfectly normal and we continue to think that she would be completely normal simply because therapy is safe and effective.

Obviously, what we are doing, we need to continue to follow this patient and just for your information, the Association for Creatine Deficiency has developed a registry for patients with this condition, which will allow us to gather information on the on the clinical course of all patients with cerebral creatine deficiency.

But at the same time, we think that early identification can really prevent long-term disability and prevent irreversible brain damage. And for this reason, I continue to strongly encourage expansion of newborn screening to include GAMT Deficiency in the panel. Thank you for your attention.

CYNTHIA POWELL: Thank you. Dr. Pasquali.

MARZIA PASQUALI: Thank you for allowing me to speak about newborn screening for GAMT Deficiency. My name is Marzia Pasquali. I'm a clinical biochemical geneticist at the University of Utah, ARUP Laboratories. My lab has developed and validated a newborn screening for GAMT Deficiency and has implemented the statewide screening. We also perform many of our chemical genetic tests to diagnose and monitor patients with metabolic disorders.

Today, I would like to address the feasibility of newborn screening for GAMT Deficiency from the laboratory point of view. GAMT screening is performed by measuring creatine and guanidinoacetate in blood spots using tandem mass spectrometry. This currently is the standard methodology used in newborn screening laboratories. Therefore, screening for GAMT Deficiency can be easily integrated in the workflow of any labs. It does not require additional samples, instrumentation, or personnel and the additional cost is minimal.

Laboratories may use derivatized or random derivatized methods for screening. We have demonstrated in our paper that is being published in Molecular Genetics and Metabolism, that newborn screening for GAMT Deficiency works with both methods. Second-tier tests biochemical and/or molecular area available and effective. Screening can be done effectively even if you don't have availability for second-tier test. You can modify your workflow and perhaps request a repeat screen where results are concerning or if you are in a state that generally mandates two screens, you can look at the second screen. All these approaches are described in our manuscript have very low false positive rates and therefore they don't cause an additional burden to follow-up programs.

There are validated tests to biochemically confirm or exclude the GAMT Deficiency once there is a positive newborn screen result. Genetic testing is routinely available and there are guidelines from the Medical College of Medical Genetics and Genomics for the laboratory diagnosis of this condition.

In summary, there are no technical barriers to the implementation of the newborn screening for GAMT Deficiency and this could be a very valuable addition to the existing newborn screening panel. Thank you for your attention.

CYNTHIA POWELL: Thank you. Hopefully, we've been able to locate Becky and Stu Tribe. There you are. Great. Yeah, we can hear you. Go ahead.

BECKY TRIBE: Okay. I might just give my comment.

CYNTHIA POWELL: Yes, please go ahead.

BECKY TRIBE: All right. So, my name is Becky Tribe. This is Woody Tribe. He's an 8-month-old

little baby boy and he had GAMT. So, Woody is meeting all his milestones. He is thriving, and he's a pretty average baby. But this almost wasn't the case. Sorry, I just ran up the stairs. Anyway, so Woody was supposed to be born in LA, but COVID brought our family to Utah and we ended up having him here in Utah. So, on December 4th, he was born here in Utah and after his birth, he passed all his newborn tests with flying colors and he was even allowed to leave the hospital early because he looked super healthy and great. But after being home for about three days, we had a call from our pediatrician saying that something was flagged on his newborn screening and that we would need to go and get blood work done right away for Woody.

So, the blood work all came back positive and we learned that Woody indeed had GAMT and that his body was not producing creatine on its own. So, when he was just a week old, the guanidinoacetate level in his blood was already like three times the amount of an average person. So, he needed to start supplements right away.

So, we met with the team in Utah with Dr. Longo and they started him on creatine right away. So, at four months, Woody received a full developmental assessment, and it came back that he was average and normal in every area developmentally at four months and he continues to reach his milestones and has been pretty normal. So, the crazy thing though is that if we had decided to stay in California and have Woody in LA that his life would be drastically different. We probably wouldn't have known that he had GAMT because he would not have been screened at birth and who knows at what age he would have been diagnosed, and the toxins would have just basically built up in his brain, and we wouldn't know anything until he started showing symptoms and signs, and at that point, it would be too late to remediate some of the brain damage that had

already been done. So, that's why it's super essential for the newborn screening to be done at birth for babies who have GAMT and they need to start treatment right away to prevent any of that damage.

So, we are super, super grateful that Woody was given newborn screening at birth here in Utah and that he was diagnosed so young. Doctors have hope that he'll live a really normal life aside from taking his creatine every day. He takes creatine four to six times a day and yeah, that helps regulate the guanidinoacetate level in his brain.

So anyway, Woody's story is just proof that the newborn screening is essential and that it works and that when diagnosed from birth, that these babies can start receiving the medications they need to have a normal and productive life. So, we're super thankful for that and we would just urge you to push GAMT forward on moving forward on being put on the newborn screening. Thank you so much for your time.

CYNTHIA POWELL: Thank you so much for sharing your story and thanks for Woody -- thanks to Woody for joining you today.

All right. We'll now move on to our other public commenters. Well hear from Dr. Joanne Kurtzberg, who will discuss Krabbe disease.

JOANNE KURTZBERG: Thank you. Can you hear me okay?

CYNTHIA POWELL: Yes.

JOANNE KURTZBERG: Okay. Well, thank you for giving me the opportunity to speak to the Committee today. My name is Dr. Joanne Kurtzberg, and I'm the Jerome Harris Distinguished Professor of Pediatrics and a Professor of Pathology at the Duke University School of Medicine. I'm also the Director of the Marcus

Center for Cellular Cures in the Carolinas Cord Blood Bank at Duke. I trained in pediatric hematology/oncology and started the Pediatric Blood and Marrow Transplant Program at Duke in 1990. Over the past twenty-seven years, my team and I have transplanted over 360 infants and children with leukodystrophies including 60 patients with Krabbe disease. We are now developing an adjuvant cellular therapy in an attempt to improve outcomes for patients with Krabbe disease and related leukodystrophies.

On behalf of the Hunters Hope Foundation and the Krabbe disease community at large, and as Dr. Powell announced this morning, I'm very pleased to inform you that on July 9, 2021, we resubmitted the nomination form to add Krabbe disease to the RUSP. Since the initial nomination of Krabbe disease to the RUSP failed by a vote of 8 to 7 in 2010, the Hunters Hope Foundation has created and worked closely with the Krabbe Disease Newborn Screening Taskforce to improve newborn screening methodology and outcomes. This taskforce has systematically addressed and filled the gaps identified by the Committee during the first evidence review. In the next minute or so, I'll highlight the progress made to address these gaps.

The first identified gap was lack of consensus about case definitions, particularly for early infantile Krabbe disease. Recent studies of the natural history of Krabbe disease have provided the basis of categorizing several forms of Krabbe disease with limited overlap. This led to the definition of Krabbe disease forms that could replace earlier terminology, including infantile Krabbe disease. They are infantile Krabbe disease, where there is onset of irreversible and rapidly progressive symptoms before 12 months of age leading to death before the age of 2 years. Late infantile Krabbe disease where there's onset of the irreversible and progressive symptoms

between 1-3 years of age. Juvenile Krabbe disease with onset of progressive symptoms between 4 and 17 years of age. And adult Krabbe disease, where there's onset of progressive symptoms at 18 or more years of age.

The second identifiable gap was the lack of an algorithm for screening and diagnosing Krabbe disease. Perhaps the most impactful advance in Krabbe disease newborn screening over the last decade has been the ability to measure the biomarker psychosine in newborn screening dried blood spots. Incorporating the measurement of this biomarker as a second-tier test into the screening algorithm virtually eliminates false positive results while enabling rapid diagnosis and treatment initiation for newborns with the infantile Krabbe disease. Psychosine has also immensely improved and simplified the identification of and followup protocols for children at risk for later onset forms of Krabbe disease. This has reduced the need for monitoring with invasive neurophysiologic and neuroimaging studies to predict the onset and progression of the disease.

Guidelines have recently been established and published to facilitate the diagnosis, monitoring, and treatment initiation for both infantile Krabbe disease and later onset forms. To further assist and help, we also formed the Krabbe Disease Newborn Screening Council, which meets monthly to provide newborn screening and medical professionals in states screening for Krabbe the opportunity to stay informed of best practices and to facilitate the management of complex cases including later onset Krabbe disease, patients with mild to moderately elevated psychosine levels in the absence of clinical symptoms of Krabbe disease and genotypes known to be associated with the disease.

Finally, Krabbe disease can be added cost effectively to the newborn screening programs already

screening for three conditions included on the RUSP, Pompe disease, MPS I, and adrenal leukodystrophy.

The third gap that was identified was the need for more information about treatment and relevant genotypes. As mentioned above, guidelines to support the efficient diagnosis, monitoring, and treatment initiation have been published. Moreover, treatment protocols for hematopoietic stem cell transplantation have been further improved and gene therapy trials have been recently begun. While molecular genetic analysis of GALC can be helpful in the decision-making process when a genotype is known to cause a specific Krabbe disease variant is identified, psychosine has better predictive value, especially when genotypes include variants of uncertain significance, which is a frequent occurrence.

Krabbe disease is devastating disease. Without a newborn screening, children with the infantile phenotype develop clinical symptoms as early as 2 months of age. As the disease rapidly progresses, these infants lose previously achieved milestones, cannot be fed by mouth, develop spasticity, blindness, seizures, and most tragically are very irritable and in extreme and constant pain. Many parents report that during this stage of the disease, their child screams inconsolably for up to 20 hours a day. Meanwhile, parents search desperately for a diagnosis and once established, it's too late for their symptomatic child to undergo treatment beyond attempts at palliative care until their death, which typically occurs by their second birthday.

Newborn screening for Krabbe disease brings new hope to this otherwise horrific disease. Currently, nine states are screening for Krabbe disease with additional states working towards its implementation. Whenever possible, these programs are moving towards or

implementing the screening protocol recommended in our submitted nomination form that detects virtually all cases of infantile Krabbe disease and likely the vast majority of individuals at risk for later onset forms of the Krabbe disease.

There are also medical -- multiple medical centers across the country able to treat affected newborns with hematopoietic cells -- stem cell transplantation, ensuring that treatment is accessible to all who need it.

Children with infantile Krabbe disease identified through newborn screening are able to undergo transplant within their first weeks of life. These children live for decades and can move independently, attend school, play, laugh, eat, speak, and most importantly, they're alive and active members of their families.

Clinical trials for additional treatment options for Krabbe disease are underway, making the future for children identified through newborn screening more hopeful than ever before.

After fifteen years of newborn screening for Krabbe disease and nearly 30 percent of US newborns now being screened for Krabbe disease annually, we firmly believe that it's time to add Krabbe disease to the RUSP using the effective and efficient screening approach outlined in the recently submitted nomination package. The consequence will be equitable access to timely and lifesaving treatment for every child in the United States with Krabbe disease while minimizing the negative impact of false positive results.

We look forward to your review of our nomination package and sincerely thank you for the opportunity to share this information today. Thank you.

CYNTHIA POWELL: Thank you, Dr. Kurtzberg. We'll next hear from Elisa Seeger.

ELISA SEEGER: Hi. My name is Elisa Seeger and I'm -- oh, sorry -- the founder of the ALD Alliance. I started the ALD Alliance after losing my son Aiden to ALD in 2012 and I want to than the Committee for having ALD added in 2016.

Dear Chairwoman Powell and members of the Advisory Committee for Heritable Disorders in Newborns and Children. On behalf of the over 30 million Americans living with rare disease and as co-chair of the EveryLife Foundation's Newborn Screening and Diagnostics Working Group, I am pleased to offer the following comments to inform the Advisory Committee's ongoing conversations about the review process for new RUSP nomination packages.

The EveryLife Foundation for Rare Diseases is a nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to advocate for impactful science-driven legislation and policy that advances the equitable development of and access to life-saving diagnoses, treatments, and cures.

Community Congress is a forum for collaboration across stakeholders, representing over two hundred individual rare disease patient advocacy organizations in addition to over ninety other health care and biotechnology organizations. Our Newborn Screening and Diagnostics Working Group is dedicated to ensuring that the rare disease community receives the earliest possible access to lifesaving diagnostic opportunities through newborn screening and other diagnostic tools.

We understand that the periodic evaluation of the RUSP nomination process is necessary to ensure that standards are current and rigorous. We appreciate that the Advisory Committee sought out input from the

patient community multiple times during its review process and are continuing that practice today.

Our communities worked for many years with relevant partners and experts to develop a newborn screening system that includes the dried blood spot screening, confirmatory testing, educational materials, and followup infrastructure for our respective disease communities.

This requires investment in developing care standards and screening tools, conducting pilots, and then leading the compilation of a nomination package that meets the evidentiary requirements for the RUSP.

To inform their activities, we offer the following comments.

On the condition nomination form, what additional information would better inform the Committee? Recognizing this significant workload of the Advisory Committee and the pipeline of conditions that may be nominated to the Committee in the near term, we urge you to consider the following recommendations for additional information on the condition nomination form.

The assessment of the benefit of screening for new conditions should accept a degree of uncertainty regarding the amount of data available following the approval of a treatment or the availability of an intervention and include all sources of information such as patient community insights. Parallels can be drawn from the review and regulation of treatments where FDA weighs such factors in order to speed the availability of new treatments for serious or life-threatening diseases to address unmet medical needs.

The use of long-term data plays a vital role in understanding the potential impact of conditions being considered for RUSP nomination. The use of long-term

newborn screening data can help to close health equity gaps, improve health outcomes, and form earlier clinical care guidelines, and improve important data to guide health policy.

The creation of a central database for review of long-term data would provide the Advisory Committee the ability to track incoming data for conditions planning to submit a RUSP package.

Many patient organizations are leading longitudinal data collection efforts within adjacent ecosystems and would be critical and eager partners in this endeavor.

What information is difficult to obtain? If a child's disease is not picked up via newborn screening, they often go years without an accurate diagnosis. Opportunities to study a treatment or intervention in infants and young children are limited as a result. In the absence of early detection, it is challenging to obtain data for certain decision-making criteria requested to demonstrate the benefit of earlier diagnosis. That same data is often required when submitting a RUSP nomination form.

Successful RUSP nominations require prospective population-based pilots that may cost millions of dollars and take several years to complete. It may not be feasible for many patient organizations to shoulder the financial responsibility of building a framework for a newborn screening pilot.

Other diseases are so rare that conducting a state pilot that satisfies existing decision-making criteria may not be feasible.

The same challenges associated with developing a treatment for rare disease will exist when assessing the benefit of newborn screening. Disease rarity, heterogeneity, and other disease-specific

considerations may impact the ability to assess the benefit of newborn screening within a population.

The decision matrix is a tool to assist the Committee in making decisions. Are there suggestions for additions or edits on the decision matrix?

When approving a condition, the Committee must consider that not all rare diseases will follow the same trajectory. Some diseases, when left untreated, may result in death within the first 5 years of life. Many other rare diseases are progressive and equally devastating with irreversible decline beginning early in life. In such cases, clinical outcomes may take years to measure and newborn screening provides a gateway to improve current treatments and develop new ones that will stop at decline.

We urge the Committee to update the decision matrix to account for the variability in disease trajectory when considering the benefits of newborn screening. We appreciate that the COVID-19 pandemic has placed even greater demands on the precious commodities of time and resources on our newborn screening leaders and we are especially grateful for your unwavering dedication to our rare disease patient communities. The EveryLife Foundation and the membership of our Community Congress Newborn Screening and Diagnostics Working Group stand ready to support your work and we look forward to engaging with you over the next several months. Thank you for the time.

CYNTHIA POWELL: Thanks very much.

We'll next hear from Dean Suhr from the MLD Foundation.

DEAN SUHR: Good afternoon, Dr. Powell and Committee Members. Thank you always -- as always for your hard work on behalf of those families with disorders detected. We'd also like to thank the

Committee for the extensive and informed process you are undertaking to review the current RUSP review process and the last two years of effort.

We just heard a great summary and recommendations from EAP. Thank you, Dr. Kemper, and that team for your thorough work.

We would like to acknowledge EveryLife Foundation, the Rare Disease Community Congress, Newborn Screening and Diagnostics Working Group's statement and we're in full support of the comments they just submitted, and we're pleased to have actively participated in this process.

But we feel we must highlight that as the Advisory Committee keenly focuses on the thorough evidence-based review using a structed process with a high bar, the clock keeps clicking, advocacy gathers data through pilot studies, lab defer implementing new screens, millions of babies are not screened, babies miss out on available therapies, and many babies are significantly disabled and die. Emerging and approved therapies are of no value if they're not accessible and if patients are not identified in a timely fashion. Newborn screening is a critical part of that identification.

What Dr. Powell and Dr. Kemper just shared is ACHDNC 2.0. What I'm sharing, perhaps, is 2.1 or 3.0, i.e. we're already talking about considering the next generation of potential systemic changes while you're just now considering and digesting the last two years of work. We believe this is required to address the reality of the tsunami of new conditions and therapies that are forthcoming. We need these discussions and creative considerations to start now.

Dr. Shone, I think, opened the door to this as well. These comments were written before we knew what the information was this morning.

Over the last decade, the FDA has been learning how to maintain their high standards while incorporating the patient voice and better understanding the unique needs, tolerances, and priorities of each disease community. We ask the Committee to consider how they can maintain their high standards while adapting to these same uniqueness and priorities when considering review of a nomination.

Further, we urge you to consider how committee reviews might be redesigned without sacrificing quality to address the historically decades long serial process of research, clinical trials, FDA approval, RUSP nomination, and then finally public health implementation.

We believe the near-term impact on babies can be greatly improved if the new nomination starts with a high value of baseline data, undergoes thorough Committee review, and then we jointly determine the safest and most effective way to implement broad public screening with the knowledge that there might be uncertainties and risks that can be reduced and managed as we continually learn, improve, and adapt over time. This approach requires near- and long-term followup and data to continually improve the system.

COVID has taught us we can save hundreds, if not thousands and millions of lives, by being proactive and using informed emergency vaccine approvals and then moving to full vaccine approvals. We're not suggesting emergency approval for newborn screening, but this sort of continued improvement has proven to be an effective and efficient mechanism.

Do remember that newborn screening is a key and timely diagnostic step, not an irreversible therapy. There will not be too many babies identified in the first year or two of an expedited new screening that increased diagnostic and therapeutic decision-making oversight cannot be incorporated during this time frame; i.e. we can learn as we go.

In the MLD community, there's a phrase; time is neurons; once lost, it cannot be restores. There are an estimated one hundred babies born per year in the US with MLD. Stem cell transplant has been proven to be an effective therapy for some pre-symptomatic MLD patients and some lucky babies who have older -- and lucky I say in quotes -- who have older siblings with MLD accessing MLD gene therapy, which has been approved by the AMA last year. They are accessing it through a compassionate-use program here in the US, while biopharma is actively engaged with the FDA for US review and approval.

As part of refining the current MLD newborn screening, we've screened over 100,000 babies here in the USA. The biochemistry and genomics on newborn blood spots have proven the screening works. In fact, they found two babies. But this data was not gathered on identified babies. So, that block on the nomination form remains blank, while we ramp new pilots and essentially start over to regather data.

Our current pilot programs might only identify one or two of these sick children each year while we undergo the Advisory Committee nomination review process. The rest of these children will not be diagnosed and will die from MLD while our nomination data gathering is underway.

MLD Foundation would be willing to have a very serious discussion with the Committee or one of the subcommittees on behalf of the existing and to-be MLD

community to show how we might be a prototype to design and test new paradigms for RUSP approval if it will satisfy the Committee's high bar for volume and confidence in data while balancing and incorporating the risks, priorities, needs, and lives of the babies and their families.

A quick comment about the RUSP Round Table, an initiative that we launched in 2015. It is disease agnostic and looks at the entire newborn screening ecosystem. The goal of the RUSP Round Table is to create an open, well-informed space to share perspectives and insights from key experts in the newborn screening space, expand the common knowledge base, and identify opportunities for both coalition building and collaborations across sectors to innovate and accelerate programs to make newborn screening more robust and equitable.

We've been on hiatus while the Advisory Committee has been meeting virtually. However, in anticipation of meeting again in person in early 2022, we'll be meeting virtually in November to regroup and refocus our efforts, and what the Committee has shared today will be part of the fodder for that discussion. You can learn more about that at rusproundtable.org.

Again, thank you for your ongoing hard work in this area of public health that's so critical to over 4 million US babies born per year and informs the screening for millions of others in other countries. Thank you.

CYNTHIA POWELL: Thank you. Finally, we'll hear from Liesl Broadbridge from the EveryLife Foundation for Rare Diseases.

LIESL BROADBRIDGE: Hi everyone. My name is Liesl Broadbridge and I'm the policy fellow for the EveryLife Foundation for Rare Diseases. On behalf of

the EveryLife Foundation, I would like to thank the Committee for providing us with the opportunity to present comments here today.

EveryLife's Newborn Screening Initiative is focused on ensuring babies receive lifesaving treatment opportunities through early diagnosis with newborn screening.

This year, our foundation's newborn screening policy work has continued to focus on efforts to align federal RUSP recommendations with state implementation and to support stakeholders' preparation for RUSP nomination through capacity-building efforts.

With respect to our RUSP alignment legislation, I'm pleased to share that with broad legislative and executive support this spring, the governors of Georgia, Ohio, and Arizona have signed into law legislation that will require the states to screen newborn babies for any disorder on the RUSP.

In addition, North Carolina's House of Representatives passed similar legislation in May and is now pending Senate action. We are in the planning phase for 2022 state efforts and look forward to working with the community to enact additional lifesaving legislation next year.

With respect to supporting stakeholder engagement and capacity-building, the EveryLife Foundation is again delighted to partner with Expecting Health to host the 3rd Annual Newborn Screening Boot Camp this fall.

Our virtual program will again provide resources and unique opportunities for cross-sector engagement with community stakeholders about the overall newborn screening system, the RUSP review process, opportunities for addressing racial inequities within newborn screening, and much more. We appreciate

the time and dedication of the expert speakers and community members who will be part of this event.

As you heard previously, the foundation is proud to serve as the convener of the Community Congress Newborn Screening Working Group in addition to comments you heard from Ms. Elisa Seeger today, we would like to share that our membership urges continued emphasis and attention to the resources and communication efforts that will be necessary to help relay updates from the Committee's condition nomination, evidence review, and decision-making processes.

As you know and we've already discussed today, revisions to the evidence review process will impact stakeholders across the newborn screening system and changes to data requirements will impact the design of studies conducted for a RUSP nomination package and any review of current RUSP conditions will require additional oversight and data reporting for state newborn screening programs.

For these reasons, we suggest that the Advisory Committee create a suite of educational materials for newborn screening stakeholders identifying changes to the evidence review process and how those changes will impact specific components of the newborn screening system. And to accomplish these educational goals, we encourage the establishment of a multi-stakeholder working group including representatives from the patient community to help inform the development and dissemination of these materials.

Thank you again to the Advisory Committee for your tireless efforts on behalf of our nation's newborns. We are encouraged by all of the great work that is occurring within the newborn screening space, and we look forward to continuing to help advocates

effectively navigate and engage with the newborn screening community. Thank you.

CYNTHIA POWELL: Thank you. And thank you to all members of the public for taking time to provide your comments to the Committee.

We'll now take about a 19-minute break and reconvene at 1:20 Eastern time -- that's 1:20 Eastern time. Thank you.

BREAK

CYNTHIA POWELL: Welcome back. I think we're ready to get started again. Before we reconvene and begin the Nomination and Prioritization Work Group Summary of the GAMT Deficiency Nomination Package, I will take attendance again.

From the Agency for Health Care Research and Quality, Kamala Mistry.

KAMILA MISTRY: Here.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Here.

CYNTHIA POWELL: Jeff Brosco.

Kyle Brothers.

KYLE BROTHERS: Here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: Representing the Centers for Disease Control and Prevention, Carla Cuthbert.

CARLA CUTHBERT: I'm here.

CYNTHIA POWELL: Representing the Food and Drug Administration, Kellie Kelm.

KELLIE KELM: Here.

CYNTHIA POWELL: Representing HRSA, Michael Warren.

MICHAEL WARREN: Here.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Here.

CYNTHIA POWELL: Representing the NIH, Melissa Parisi.

MELISSA PARISI: Here.

CYNTHIA POWELL: I'm here. Annamarie Saarinen.

ANNAMARIE SAARINEN: Here.

CYNTHIA POWELL: And Scott Shone.

SCOTT SHONE: Here.

CYNTHIA POWELL: For our organizational representatives, from the American Academy of Family Physicians, Robert Ostrander.

ROBERT OSTRANDER: Here.

CYNTHIA POWELL: The American Academy of Pediatrics, Debra Freedenberg.

DEBRA FREEDENBERG: Here.

CYNTHIA POWELL: American College of Medical Genetics, Maximilian Muenke. American College of OB/GYN, Steven Ralston. Association of Maternal and Child Health Programs, Jed Miller.

JED MILLER: Here.

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

SUSAN TANKSLEY: Here.

CYNTHIA POWELL: Association of State and Territorial Health Officials, Chris Kus.

CHRISTOPHER KUS: Here.

CYNTHIA POWELL: Association of Women's Health, Obstetric, and Neonatal Nurses, Shakira Henderson. Child Neurology Society, Jennifer Kwon.

JENNIFER KWON: Here.

CYNTHIA POWELL: Department of Defense, Jacob Hogue.

JACOB HOGUE: Here.

CYNTHIA POWELL: Genetic Alliance, Natasha Bonhomme.

NATASHA BONHOMME: Here.

CYNTHIA POWELL: March of Dimes, Siobhan Dolan.

SIOBHAN DOLAN: Here.

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

CATE WALSH VOCKLEY: Here.

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

GERARD BERRY: Here.

CYNTHIA POWELL: Thank you.

The Committee received a nomination to include Guanidinoacetate Methyltransferase Deficiency to the Recommended Uniform Screening Panel. In terms of the nomination process, the first step is for HRSA to conduct the initial review for completeness. After it's been determined that the nomination package has all of the required components, the Nomination and Prioritization Work Group reviews the information submitted in the package and provides the Committee with a summary and recommendation as to whether or not the condition ought to move forward to a full evidence

review. The Committee will then vote to assign or not assign the nomination condition to the External Evidence Review Group that conducts the evidence-based review. GAMT deficiency has been nominated again for inclusion on the RUSP. Next slide.

The last time it was nominated in 2016, the Committee voted not to move GAMT deficiency forward to full evidence review. Nominators were informed that while the Committee recognized that GAMT deficiency is a "medically important disorder that deserves serious consideration," the Committee's decision to not send the nomination forward for evidence review was "based primarily on the determination that the analytic validity of the screening test had not yet been determined, in part because no cases had been identified prospectively through newborn screening."

Today, on behalf of the Nomination and Prioritization Work Group, ex-officio Committee Member, Dr. Carla Cuthbert, will present the summary and work group recommendation to the Committee. Next slide.

Dr. Cuthbert will review this in her presentation, but I would like to remind the Committee that at this phase of the nomination process, there are three core requirements for a condition to be considered in addition to the information requested on the nomination form. The validation of the laboratory test, that there's widely available confirmatory testing with a sensitive and specific diagnostic test, and finally, that there has been a prospective population-based pilot study.

By way of introduction, Dr. Cuthbert is the ex-officio member from the Centers for Disease Control and Prevention, where she is the Chief of the Newborn Screening and Molecular Biology Branch in the Division of Laboratory Sciences, National Center for Environmental Health. She has held this position since

December 2009. Dr. Cuthbert gives leadership and oversight to the Newborn Screening and Molecular Biology Branch, a branch that comprises several laboratories, which support newborn screening programs by providing quality assurance materials, public health service, and technical expertise, test development, and translational research activities. I would now like to turn it over to Dr. Cuthbert.

GUANIDINOACETATE METHYLTRANSFERASE (GAMT)DEFICIENCY NOMINATION SUMMARY

CARLA CUTHBERT: Thank you very much Dr. Powell. It's a pleasure to be able to speak on behalf of the Nomination and Prioritization Work Group and to present our findings as a result of the package that was submitted to us.

The work group comprises the individuals that you see on the bottom left and again, I'd be happy to present our discussions and deliberations. Next slide. Next slide, please. Thank you.

So, the nominators, we've heard from them today, so Dr. Nicola Longo is the nominator, the co-sponsoring organization is Dr. Marzia Pasquali from the University of Utah and ARUP Laboratories, and the advocate organization associated with this nomination is the Association for Creatine Deficiency. Next slide, please.

The Creatine Synthetic Pathway is shown on the right of this particular screen. I hope that you can see it clearly. Essentially, Guanidinoacetate Methyltransferase or GAMT is one of the enzymes involved in the synthetic pathway for creatine. It first starts off with an enzyme called AGAT or the L-arginine glycine amidinotransferase enzyme that transfers an amidino group from arginine to glycine to form the guanidinoacetate.

GAMT, the enzyme methylates guanidinoacetate to form creatine and creatine can be taken up by tissues through the creatine transporter and creatine within many of these tissues can function to help regenerate ATP and ADP from ADB in tissues that have really high energy requirements. So, it plays a very significant functional role there and it's also -- it also functions as a neurotransmitter in the CNS.

Of note, it's very important to know that about half of the creatine in the body is derived from this synthetic pathway, and the other half is derived from dietary sources such as meat and fish. Next slide.

So, in terms of the biochemical derangement in GAMT deficiency, mutations -- either homozygous mutations or compound heterozygous mutations in the GAMT gene can result in GAMT deficiency. Again, this is one member of a three-member family of cerebral creatine deficiencies and the pathophysiology that is observed with this particular condition, especially the biochemical phenotype, results in a reduction in creatine and marked increase in the neurotoxic guanidinoacetate.

If we look at both plasma and urine, GAA is elevated in both the plasma and in the urine. Creatine is decreased in plasma and it could be anywhere between the normal range or reduced in urine. The ratios for GAA over creatine are generally elevated in patients that have this disorder. Next slide.

As far as the clinical presentation, the onset of patients with this disorder occurs anywhere from the first few months to the first few years of life, and the clinical presentation we heard from Dr. Nicola Longo involves a number of -- of clinical features such as cognitive impairment, developmental delay, and speech delays, hypotonia. Some of the patients will experience seizures of varying degrees of severity,

movement disorders, and various behavioral abnormalities, which can include autism spectrum abnormalities as well as auto-aggressive behavior. Next slide.

In terms of management or treatment rationale for patients who have this disorder, there are two significant approaches that are used. The first is to restore the creatine pool. So, if you've got a blot with GAMT, you really want to be able to take a look at what's reduced, which is the creatine supplement through higher doses to be able to increase the amount of creatine available and also supplementation of S-adenosylmethionine as well.

In addition, we want to be able to reduce the accumulation of guanidinoacetate and we can do this by reducing -- sorry, by increasing or supplementing with ornithine and reducing arginine and also by adding sodium benzoate, which can function to bind and help with the excretion of any glycine that accumulates in this disorder. Next slide.

So, the core requirement, as Cynthia indicated, was that we need to have some appropriate clinical tests, laboratory screening tests. There needs to be some sort of diagnostic test available and really what's very, very critical is that we need to have a population-based study or some -- some kind of routine screening activity. Next slide, please.

Today, we're going to evaluate these questions here. There are eight questions that are used to further identify, again, the suitability of this package for moving it forward. You've probably seen this slide before. We discussed this when we were addressing MPS II in May. So, essentially, we really want to know if the condition is medical serious. Is there case definition? We want to understand about the prospective pilot and pilot data. We want to make sure

that the screening test has appropriate analytic validity and determine whether or not the characteristics of the screening test are appropriate for the high throughput newborn screening system that we've got with particularly a low rate of false negatives.

We want to ensure that there is some kind of diagnostic confirmatory testing process, there is -- there are appropriate treatment and management approaches for the newborns that would be identified with this condition, and we want to understand the clinical utilities. So, after we've identified the newborn, will -- will there be benefit as a result of the intervention that we will be -- that will be -- that the child will undergo. Next slide.

So, we're going to go through these one by one. So, the first question is, is the nominated condition medically serious. I think I had a bit of help from some of our -- the individuals who spoke during the public session, but yes. The nominated condition is indeed very medically serious. It is a health condition with a very high risk of morbidity that will negatively impact daily function and quality of life and I just went over the clinical presentation earlier and again, these are -- appears to be nonspecific. So, again, the point is that it may not be entirely apparent when these -- when this presentation -- when these newborns or children have this presentation to be able to do this testing. So -- so, it is medically serious. Next slide, please.

Number two, is the case definition and the spectrum of the conditions -- condition well described to help predict the phenotypic range of the children who will be identified based on population-based screening. And again, the answer here is yes. This is an autosomal recessive inborn error of creatine

synthesis. The clinical presentation reflects the importance of creatine in the central nervous system. We just discussed about clinical features and the cognitive impairment, the developmental delay, and so on that these children will have. And so, again, both of our chemical and the clinical features have been described in various papers.

We, as part of our deliberation and discussion, did note as we would expect with other newborn screening conditions, that GAMT is a very rare condition. So, while we do have a very good understanding of the clinical and biochemical features, the full spectrum of the phenotypic presentation will become more evident the more the newborn screening becomes more widespread. So, the point is, we still have much that we can learn as a result of the impact of newborn screening scenarios.

So, yes, and again one of the points that we did bring up as well is that is it possible that there are older patients who have some of these nonspecific clinical presentations who remain undiagnosed that are part of our population and that have gone undiagnosed. So -- so, this is a question that we did ask as well. So, we do have much to learn, yet we do have a very good understanding of how these kids will present. Next slide, please.

So, the third question is are there prospective pilot data from population-based assessments available for this disorder. In this particular case, the ongoing population-wide screening activities are not pilots. They are actually incorporated as part of routine testing for two states and two programs in two other countries. So, in the states of Utah and New York, these are routine population screening activities that began in 2015 and 2018 respectively. In British Columbia and Canada, screening began in 2012 and in

Victoria, Australia, about twenty years ago they have been screening for this condition as well. So again, these are -- and again, they -- they do have very similar testing approach. You -- we have the number of newborns that are screened here and again, it was mentioned in the public time that we do have two positive newborn -- two newborns that were identified in Utah and New York.

Just of note, I did check in with our colleagues from British Columbia and Victoria, and they have confirmed that they have not yet identified a newborn with this particular condition. In my conversation with Dr. James Pitts from Victoria, again, he said he does not have any explanation as to why he's never -- they have never identified a case. I don't believe that they will stop screening. It's -- it continues to run attached to the amino acid acylcarnitine test platform, and it does not have a significant number of false positives attached to it. So, they -- they are happy to continue with -- with testing.

So, again, there is data associated here and I just again wanted to make sure that you guys saw that. Next slide.

With respect to the two cases -- the two newborns that were identified positively with GAMT deficiency, these next two slides will just briefly describe some of the data associated with that. Here we have the Utah case -- and again, we were privileged enough to hear from, I believe, Mom Becky -- I didn't catch your name, Becky -- but this is about the newborn that was identified here. What you're seeing here in the left-hand panel are the newborn screening and diagnostic results on the left. So, Utah, for a period of time between June 2015 and May 2019, used a derivatized newborn screening testing approach and they

eventually moved to a nonderivatized newborn testing approach, and these two rows just show the data associated with the total number of newborns tested in their state during that period of time. It's a two-screen state. So, they did have -- they do have a normal range for what's expected for the guanidinoacetate or GUAC here and the CRE is the creatine that was evaluated. And so, we have that for the first- and second-tier -- the second routine tests and of note, with the patients that tested positive, we can see that the concentration of the guanidinoacetate was markedly elevated in both of the testing samples at 13.25 and at 9.26 and the creatinine again in this particular case you may not see it being too significantly reduced -- it was a little bit more reduced on the second sample. But when we went to -- when they went to the diagnostic follow-up, I think it was a little bit more evident there that the guanidinoacetate in plasma was elevated at 9.16 with a normal range having an upper limit of 1.8 and the creatinine was significantly reduced with normal range as shown here from 37-117.

Management and outcome for this newborn therapy was started on day 11 and again, as was indicated in terms of the clinical management, creatinine and ornithine supplementation was given, sodium benzoate was -- was given as well to remove glycine, and then there was moderate protein restriction as well.

With the current status of the newborn, I think that we actually saw baby Woody. So, he remains normal. He is growing and developing well and tolerating his therapies. Next slide, please.

In a similar vein, we have some information about the New York newborn that tested positive. New York is a single-screen state. We have here an indication that they screen for just over half a

million newborns during the period of time from October 2018 to the time of the writing of the manuscript here and again, for the patient that screened positive, the guanidinoacetate was 23 with the references ranges you see here.

The diagnostic follow-up again showed a marked elevation in plasma levels of guanidinoacetate and reductions in the creatine in the plasma as well.

In a very similar manner, management and outcome were very, very similar to the Utah newborn and in this particular case as well, this newborn is tolerating therapy well, growing and developing normally. Next slide, please.

So, does the -- question number four is does the screening test have established analytical validity. And I just wanted to again point out that in terms of screening tests, the primary newborn screening assay essentially could be multiplexed with the amino acid and acylcarnitine analysis. It could be derivatized or nonderivatized. At this point in time, there is no FDA-approved kit. So, all programs that are interested in bring this up would have to develop laboratory-developed tests with the appropriate biomarkers.

A second-tier test involves liquid chromatography involved so that they could separate out any -- any interference if there is one. But again, this is another approach for being able to detect guanidinoacetate and creatinine. It can be a standalone test or multiplexed with other second-tier markers. And, of course, sequencing is also available for these programs to detect the mutation. Next slide, please.

Oh, yes. And so, the answer to this question, does it have established analytic validity, the answer

is yes. When we reviewed the performance measures, we found that it did demonstrate acceptable levels of analytic validity for both of the programs. Next slide.

Question number five is are the characteristics of the screening test reasonable for the newborn screening system, among other aspects, is there a low rate of false negatives. So, again, the biomarkers can be multiplexed. As I've indicated before, there are second-tier tests available to reduce false positives. And in speaking to all of the programs, they have all indicated there are no known false negatives that have been identified in their programs. All of them have essentially had -- they have a close relationship with the metabolic programs within their respective states or provinces so that if there is a clinically ascertained individual with this particular condition, they would be made aware of this so that they would understand and to date, there has not been a false negative case identified.

So, again, another question is given the nonspecific clinical features, is there a level of certainty that you would be made aware of all of the missed cases. I think Dr. Nicola Longo again pointed out to the -- to the fact that these -- there are nonspecific features. So, unless a clinician has -- follows up on this case to do the appropriate testing, again, you may miss it. But that does not apply here. We're talking about having screened -- will you -- are there any cases that are false negatives, and to our knowledge, the answer is no. Next slide.

So, when we were looking at some of the data associated with the characteristics of this screening test, we took a look at the -- the performance -- some of the performance characteristics from the Utah program together with the New York program and one of

the things that drew our attention was the number of screen-positive cases for New York. Again, Utah has -- is a two-screen state. So, they -- they have been -- based on their data, the total number of false positives are really low. But, you know, the high number of referrals here did cause us to ask the question about whether or not there was some underlying reason for the high number of positive cases in New York, whether or not there was an interference. And as part of our deliberations about time, we found that that was unclear and again, if this moves towards evidence review, it would be very helpful to get clarification on that information.

We have since had an opportunity to follow-up with New York, and if you go the next slide, please.

We did find out from New York that -- that there was an interference and during, I believe it was during 2019, I believe, they made some modifications to their existing test because of the number of screen positives to eliminate an interference that they had identified and I just in the left table that you see here identified in red, the product ion that was used in the assay was modified for the guanidinoacetate. It was modified from 101.1 to 73.1 and the internal standard was as well and with that modification, they did some testing to evaluate the change and to make sure that none of the other biomarkers that they were testing in this multiplexed assay were impacted. They validated the procedure based on that change and the revised method was implemented into routine testing in 2020.

And what we have on the right part of the panel here is just an indication of the performance of the -- of the -- just the number of parameters when you looked at the original method versus the revised method. And they looked at similar periods of time in those two

years, and you can see that the total number of samples screened were fairly similar and for the number of samples that required a second-tier test in the original method, they had 1,800. That was markedly reduced to -- in the revised method to 35. When you looked -- they looked at the number of repeat testing that they needed for the original method, it was 136 and with the revised method, it was 17. Those samples that required DNA testing and referral for the original method at that time was 7 and that went down to 1 for the revised method. So, again, marked improvements in their testing performance and it really did have a significant impact on their performance -- the performance of their testing. So, next slide, please.

So, is there widely available CLIA or FDA-approved confirmatory test or diagnostic testing process, and the answer is very much yes. We have listed all of the laboratories that have confirmatory tests available for GAMT deficiency here. So, yes. The answer to that is yes. Next slide, please.

Question number seven is are there defined treatment protocols and FDA-approved drugs and is the treatment -- and is the treatment available. Again, on the left-hand side, I described previously the treatment rationale for this particular disorder, and generally again, these are -- these are reagents that are available. Again we -- when we were thinking about this, there was a question as to the level of availability of these supplements. Would they be classified as metabolic foods and would -- would that provide -- would that be a challenge to any of them? Again, as part of the writeup, the nominees indicated that you can -- that many of these supplements are easily accessible and -- and they are for the most part very much available to those that most insurances will cover the costs with proper preauthorization.

In terms of treatment outcomes, symptomatic patients have been shown to improve. Patients treated earlier in life have normal or near-normal development and treatment interruption may result in irreversible damage. So, it's really important to maintain these children on treatment for life. Next slide. So, the answer for that is yes.

And the last question is, do the results have clinical utility and essentially, I mean, you know, in the likelihood of a positive newborn screening test for these newborns, this will prompt intervention. Will this intervention have a positive outcome benefit or improvement outcome? I do have here on the left-hand side a number of papers that have described studies that have documented reports about clinical improvements after treatment in patients with this disorder and again, it -- there are promising reports that describe benefit of pre-symptomatic treatment of diagnosed patients. Will you go to the next slide.

I know the next slide is a little busy. I'm sorry about that, breaking every rule about presentation. But really, the bottom line here is that in this cohort of forty-eight cases here, one of the things that we would notice is that there are about eighty -- thirty-eight families and -- and it includes younger siblings that were identified as a result of -- of an indexed patient with GAMT deficiency. And for -- for those younger siblings who were able to be treated at an early stage -- and we have examples of them in the top three -- I know situation may not be perfect -- but the -- but the data shows that -- that these individuals in the top three that -- that had treatment onset less than 4 weeks of age, they had -- they didn't have any clinical features at the time and at the time of -- of the assembly of this paper, their outcome -- their presentation was -- was clinically normal.

And I just -- I also do want to point out that we just heard from Kim Tuminello and Heidi Wallis and again from Becky, who all had -- have this similar scenario with an older affected infant and a younger child that benefitted -- sibling that benefitted from that knowledge that also has a very good outcome for the second child.

So, and I think that that's all that I want to say for this particular slide. Essentially, the three patients that are treated within one month of birth appeared normal before treatment and afterwards, the premise here again -- the summary here is that if started before 4 weeks, intellectual disability can be prevented. After 4 weeks or after the onset of treatments, treatment can still be effective, but it may not reverse intellectual disability and so again, pointing to the importance of having early treatment. Next slide.

So, the answer to the question -- next slide please. Thank you. So, the answer to the question do the results have clinical utility, the answer is yes, that there is benefit as a result of early identification and pre-symptomatic intervention. This will result in improvement in health outcomes.

And so, based on all of this, if you go to the next slide, we did have the summary here where the answers are essentially all yes. I know that we have an unclear here for number five, but again, in speaking to New York, you know, we did get some clarification on that particular issue. So, there were yes answers for all of these and that takes us to what the recommendation of the Nomination and Prioritization Group actually was, and would you mind going there.

So, as far as the Nomination and Prioritization Work Group, our deliberations would be that we recommend the Advisory Committee to move forward with

full evidence review for the GAMT deficiency in its bid for nomination to the Recommended Uniform Screening Panel.

That's all I have and thank you for listening.

COMMITTEE DISCUSSION AND VOTE ON MOVING GAMT DEFICIENCY FORWARD TO FULL EVIDENCE REVIEW

CYNTHIA POWELL: Thank you, Dr. Cuthbert, and thank you to the other members of the Nomination and Prioritization Work Group.

Now, I'd like to open it up to questions and comments, again from Committee Members first followed by organizational representatives. Again, please remember to use the raise hand feature. I'll call on you in order of when you raised your hand. Please remember to unmute yourself, speak clearly, and state your first and last name before speaking.

Any Committee Member with questions or comments? Jane DeLuca.

JANE DELUCA: Hi. Thank you for the presentation. Dr. Cuthbert, I just have one question. From the slide, from that study of, you know, the multiple cases, the third patient seemed to have a break in treatment and it seemed like the outcomes were not quite as good as in the beginning when treatment was initiated. Can you speak to that at all?

CARLA CUTHBERT: So, you are right and I know that this was not the perfect representation, but this does point to the fact that treatment needs to be maintained for these newborns. So, it is not advisable to have a break in treatment.

JANE DELUCA: And you don't have any idea how long that break was?

CARLA CUTHBERT: I do not. I apologize. I'm just trying to take a quick look here. I don't. I don't offhand. I do not, I'm sorry.

CYNTHIA POWELL: Any other questions or comments from Committee Members?

All right. Shawn McCandless.

SHAWN MCCANDLESS: Sorry, I -- just quickly. One of the advocates who was speaking to this topic this morning was making the point that this is a very rare condition but that it doesn't matter how rare it is, it should still be screened. And I guess I'm just curious if there's any -- if we have any guidance or what the thinking is about that -- that concept that -- that the rareness of the condition shouldn't matter for adding conditions to the RUSP. And I'm just curious to hear perspective from anyone who wants to weigh in.

CYNTHIA POWELL: Mei Baker, do you want to address that -- Shawn's question or do you --

MEI BAKER: Yes. I want to give my two cents.

CYNTHIA POWELL: Okay.

MEI BAKER: Yeah. I think it's a good point. This is my personal opinion. I don't think the rareness will prevent these being considered. But I do believe when a disease is so rare, I think the screening performed becomes really important and I think that I'm very pleased to see both New York and Utah. They have very, very few false positives. So, I think that is why I would be fine with that. Thank you.

CYNTHIA POWELL: I don't remember, Shawn, that it, you know, anything has come up in the past since I've been on the Committee regarding how rare a condition is and whether that should influence our

decision process. But others with longer institutional memory may want to weigh in.

SHAWN MCCANDLESS: Also to Mei's good point, which is that the more rare the condition, the more that the shift to the downside of false positives. So, the performance of the screening test becomes more and more important as the condition becomes more and more rare so you don't have an excessive number of false positive results relative to the true positives. And I wonder if there's any guidance from past discussions on that issue as well. What's a tolerable ratio of false positive to true positives?

CYNTHIA POWELL: Scott Shone, did you want to --

SCOTT SHONE: I think, yeah, I think I'll just add on to that, Shawn. Would you agree that -- so, I agree about the performance also would be the diagnostic path post-screening result and the -- and the impact and risk of that. I mean, if it's a simple diagnostic biochemistry panel or something to that effect, a very different -- and I'm not -- I'm not weighing in either way in terms of what that would be. I think it's something that we obviously need to discuss. I think it -- I think, Dr. Powell, it has come up sometimes in perhaps deliberations after the Evidence Review Group has presented in terms of some of those discussions as the conditions we look at now are rarer and rarer. So, it's again something else that will continue to come up.

I think that part of that -- part of the discussion would only -- would be not only the performance of the diagnostic test but then the next step in terms of -- the screening test -- but then the next step in terms of what the diagnostic testing regimen would potentially be, particularly if you're having more false positives.

CYNTHIA POWELL: Robert Ostrander.

ROBERT OSTRANDER: I was muted. Hi, it's Robert Ostrander, American Academy of Family Physicians. Two points. One is, I think, although we haven't stated it directly, that the Evidence Review Committee has always taken into account the rarity of the condition in that they evaluate the testing both the screening and the performance test from a perspective of positive and negative predictive value and not just sensitivity and specificity.

And the other point is that we certainly have seen some conditions where the prevalence of the disease is found to be higher once the screening is instituted. So, you know, it could be a bit of an issue, especially with rare diseases, where there's going to be, you know, the initial cases are found in a relatively small group given the rare disease that the incidence may be higher because you're suddenly doing this test on people and identifying them before they're symptomatic. We know a lot of these diseases in symptomatic individuals progress and die without a diagnosis.

CYNTHIA POWELL: Debra Freedenberg.

DEBRA FREEDENBERG: This is Debra Freedenberg, American Academy of Pediatrics. I just wanted to point out there are some conditions currently on the RUSP, and granted, they're secondary, so they're even rarer [inaudible -- muffled] still on the RUSP as a secondary.

And then a second comment I wanted to make is that even though these are rare conditions, they are routinely being seen in clinical practice by a biochemical geneticist and that as screening goes forward, they may be more common. And I'm using my own perspective. When I was in practice, I saw three kids

with this diagnosis. So, you know, my perspective of what's really rare is a little bit different. My perspective of what's really rare is you never seen them or you see once in a lifetime. But my suspicion is that there may be some undiagnosed and, you know, some of the diagnostic methods that we utilize for like MRS mass spec -- spectrometry that helps with that diagnosis. But so, I don't know that we really know. I mean, we have half a million from New York and we do have other numbers and it did take a while for the newborn screening to actually identify children. But I don't know that we really know the true incidence of this currently. I just wanted to share that perspective.

CYNTHIA POWELL: Thank you. Jennifer Kwon.

JENNIFER KWON: I appreciate what Debra said because I'm a little curious about what the recommendation is going to be for the second-tier diagnostic testing because in clinical practice, when we think about creatine deficiencies, it's -- it's usually at the screening stage where we're trying to rule out the treatable conditions, however unlikely they might be. So, we do this metabolic evaluation. And I hope the metabolic geneticists aren't appalled but, in general, getting urine on patients that you see in clinic can be very challenging. And that, as far as my understanding is, is how we generally screen for these disorders. I was actually thinking how much -- I was wondering if our yield would be higher in making diagnoses if we could, you know, get a dried blood spot specimen or actually measure creatine in blood because we're already getting blood for other metabolic testing.

So, I -- I was sort of curious about the same points that other people are raising about why are we missing diagnoses? Could we be missing diagnoses?

CYNTHIA POWELL: Shawn McCandless. Oh.

SHAWN MCCANDLESS: I just want to -- I just wanted to respond to -- first of all, thank you for all of those comments. It's very helpful. I want to respond to a couple of things that came up.

The first was the comparison to conditions that were placed on the RUSP initially. I don't think that those conditions have ever been reevaluated in a systematic the way that new additions are being evaluated and that -- therefore, I'm not sure that it's fair to say that if something is already on the RUSP, then that sets the standard for how it should be done because we've already clearly moved beyond the evidence standard from the original RUSP, and it just -- it makes a more compelling argument for why at some point there needs to be a reevaluation of those -- of those conditions in a second way or in a more -- in a more careful way with the current level of evidence review that we -- that we're applying to new conditions added to the RUSP. So, I don't think that it's -- I think we should be really careful about saying well, it's more this than this condition; it's already on the RUSP. Because those -- those historical conditions on the RUSP have not undergone the same amount of scrutiny and probably need to at some point.

The second thing is, just to be really clear, or maybe I'm misunderstanding, but the RUSP, the Recommended Uniform Screening Panel, is the RUSP. The secondary conditions is a list of conditions that are to be -- will be identified by markers that are used as primary markers for conditions on the RUSP, but they're not part of the RUSP. Is that correct? Am I understanding that correctly?

CYNTHIA POWELL: I think they're still considered part of the RUSP, but just the secondary conditions. Others may want to correct me.

MEI BAKER: This is Mei Baker, Committee Member. I think it's an ongoing discussion. I think [indiscernible] in terms that to my knowledge, I think -- well, I think it's an open discussion. Hopefully in the near future, we'll have a better sense in terms of intended targeted conditions and because when you're using a marker, you also will identify something else that needs to be well-defined -- should be well-defined.

CYNTHIA POWELL: Debra, were you going to comment before on Jennifer's question about the testing for GAMT in the clinical setting?

DEBRA FREEDENBERG: I hadn't intended to.

CYNTHIA POWELL: Okay. I thought I saw -- I thought I heard you start to say something and I cut you off.

DEBRA FREEDENBERG: Yes, it was -- I mean, she's correct. It would be -- often it is easy to do blood spot testing and collect it then on some kids. But often when you're doing evaluation for a child that does have developmental delays and seizures and you're doing a metabolic evaluation, you're collecting urine for other reasons besides looking at a GAMT evaluation. So, you'll be getting [inaudible - muffled]. You'll be doing a urine sample anyway.

CYNTHIA POWELL: Okay.

Shawn, did you have another?

SHAWN MCCANDLESS: Just to respond also to Jennifer that in the -- in a diagnostic evaluation, you're looking for other creatine deficiency disorders in addition to GAMT, and we want to be careful not to confuse the issue. This is what's being proposed for the screening panel is very specific, appropriately so.

CYNTHIA POWELL: Okay. Thank you.

I don't see any other hands raised. Dr. Berry, do you have a --

GERARD BERRY: Yes, Gerry Berry, SIMD. I wonder if you might be able to quantify this a little better because, you know, when I listen to the arguments, I -- I think -- I think of what's in favor of doing it and what's against it. So, the more -- the more rare the problem is, the less -- the less weight you would put onto it. But -- but, on the other hand, if you have a treatment that's wonderful and really, really can have a dramatic impact on that infant and child's life, that would, for me, start to push it into something that would be more, you know, more acceptable. On the other hand, if you have a lot of false positives, you know, that would be detrimental. So, I wonder if we might be able to -- to try to think of that, how you could, you know, maybe do a scoring system for this, just as a pilot -- as a pilot thing.

Of course, for us in the Biochemical Genetics Clinic, this disorder has become very important because someone -- if someone comes to us for an evaluation and they already had a pretty -- pretty significant workup, we would always measure a plasma guanidinoacetate on someone with developmental delay and hypotonia and certainly if there was a seizure problem. So, I think it's -- it's becoming more and more commonplace in the -- in the metabolic clinic.

CYNTHIA POWELL: Thank you.

Anyone else with a question or comment? All right. Is there a motion from a Committee Member regarding whether or not to recommend GAMT go forward for full evidence-based review?

KYLE BROTHERS: this is Kyle Brothers. I move that we move it forward for full evidence-based review.

CYNTHIA POWELL: Is there a second?

SHAWN MCCANDLESS: Shawn -- this is Shawn McCandless. I second the motion.

CYNTHIA POWELL: Thank you. So, we'll now hold a vote or sorry, prior to that. Is there any additional questions or comments from Committee Members only before we take a vote?

Okay. I will -- we'll take a vote and I'll read -- each Committee Member, if you could please say whether you're voting yes, no, or abstaining. Mei Baker.

MEI BAKER: Yes.

CYNTHIA POWELL: Jeff Brosco. Kyle Brothers.

KYLE BROTHERS: Yes.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: Yes.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Yes.

CYNTHIA POWELL: Kellie Kelm, FDA.

KELLIE KELM: Yes.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Yes.

CYNTHIA POWELL: Kamala Mistry, AHRQ.

KAMALA MISTRY: Yes.

CYNTHIA POWELL: Melissa Parisi, NIH.

MELISSA PARISI: Yes.

CYNTHIA POWELL: And I, Cynthia Powell, vote yes. Annamarie Saarinen.

ANNAMARIE SAARINEN: Yes.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Yes.

CYNTHIA POWELL: And Michael Warren.

MICHAEL WARREN: Yes.

CYNTHIA POWELL: Okay. We have twelve voting yes and no no's. So, the recommendation has been approved to move GAMT forward for full evidence-based review. So, we'll move that forward. I'd like to thank the Committee for their thoughtful consideration. GAMT deficiency will be assigned to the Evidence Review Group. The Committee now has nine months to complete the evidence-based review and vote on whether or not to recommend GAMT deficiency for addition to the RUSP. Thank you all.

I would next like to move forward with a presentation by Dr. Shawn McCandless about Emerging Issues in Newborn Screening. In recent months, the Committee has received public comments on the efficiency of the Committee processes for adding conditions to the RUSP. In general, these questions focused on the Committee's ability to keep pace with the number of potential nominations given rapid advancements in the detection and treatment for rare and ultra-rare heritable disorders. As you may recall, during the new business portion of the May 2021 meeting in response to public comments, Dr. McCandless asked if the Committee could have some time to discuss these issues. Given this morning's presentation on the proposed updates to current Committee processes, this is a timely conversation, and I think it's important for the Committee to engage in some forward thinking around these topics.

Dr. Shawn McCandless is a Committee Member and Professor of Pediatrics and the section head for Genetics and Metabolism at the University of Colorado,

Denver School of Medicine and the Children's Hospital of Colorado. He is a past President of the Society for Inherited Metabolic Disorders and served on the Ohio Department of Health Newborn Screening Advisory Council for twelve years prior to moving to Colorado.

Dr. McCandless' research has focused on inborn errors of metabolism and Prader-Willi Syndrome, including publicly and industry-funded clinical trials for children and adults with IEMs and Prader-Willi Syndrome. He's a fellow of the American College of Medical Genetics and is active in the SIMD and the American Society for Human Genetics.

I'll now turn it over to Dr. McCandless to take a few moments. Shawn, we're giving you thirty minutes from now for this presentation since we're starting a bit late. So, he'll briefly frame the conversation before we facilitate a discussion.

EMERGING ISSUES IN NEWBORN SCREENING

SHAWN MCCANDLESS: Thank you, Dr. Powell. Just to reassure everyone, this is not actually a presentation. It's just framing a discussion the bulk of the time will be spent on discussion. May I have the next slide, please.

Just to frame the issues, I think today's conversations earlier, the public comments, really set the stage for this discussion, and we really got into the weeds earlier today about sort of how to update the evidence review and the decision matrix, how to update them. I think what we hope will come from this conversation is sort of a step back and a look forward of what is coming down the road that this Committee is going to need to deal with, and is the system that we have in place to make those decisions going to be robust enough to deal with the -- with what's coming and specifically, as Dr. Powell alluded to, this was -- this discussion started with some questions that were

raised by public comments at our last meeting. So, some of the key considerations that we would like to discuss today and really this discussion is about the process of the Committee, is that the key considerations include sort of the tradeoffs that we make for the timeline with taking a very deliberate approach versus taking a speedy approach and specifically this morning, one public commenter actually proposed that there be some sort of expedited or expedited acceptance or approval or addition that might be time-limited. And so, that's something to consider.

The next question or the next issue to consider is the capacity of this Committee and the potential for the number of nominations in the future to outpace the Committee's capacity to do the work.

Dr. Kemper, this morning, kind of went through the timeline of the evidence review Committee, and as you can see from the amount of work that that Committee does for each evidence review, there's going to be a cap -- they have a -- a limited bandwidth to take on new -- new disorders. We've now just added GAMT evidence review while they're in the middle of doing the MPS II review, and now we have a new -- a new nomination in front of the Nomination and Prioritizations Work Group. And so this is -- this is -- it's still a small number, but based on the number of novel therapies that are in the pipeline now, heading towards getting approval, it seems likely that the numbers will increase.

And as our colleagues have brought forth the GAMT nomination has shown -- as the guidelines from this Committee become more clear, it -- the bar is higher for making a nomination, but it's also somewhat more clear what needs to be done. And so, I think it's fair to assume that there will be a fair number of more

nominations of conditions that have been not moved forward in the past will be brought back, as we saw with Krabbe Disease, and the number of nominations is likewise continue to grow.

Finally, the really important issue is around equity and specifically in this context, that question is does the RUSP nomination process favor conditions if stakeholders have more resources or conversely, does it limit conditions where stakeholders have fewer resources. So, is it fair that organizations that are larger or have more -- more funding, it's easier for them to bring a nomination than for an advocacy group or a group of patients or a group of researchers who have less funding. May I have the next slide, please.

So, some questions to start the discussion, and I would also like to invite the Committee Members and society representatives to respond to public comments that were made earlier today in addition to these questions. But just very briefly, the questions that we wanted to start with are, is the system biased towards conditions that have more resources and the followup to that is should the Committee -- should the Committee actively monitor conditions that are potential candidate for nomination rather than relying on the nomination system that we currently have?

And then, should the Committee consider a process that reviews groups of conditions at once -- multiplexed reviews -- which has been suggested by multiple people in the past as well as today. And that has then followup questions of how would this impact states and other components of the newborn screening system.

At the last meeting in May, a question was raised that if the FDA has approved a treatment, doesn't that define the condition as a treatable disorder, and so, shouldn't FDA approval automatically

make a condition appropriate for newborn screening? And that's a question that I think this group should be thinking about.

And then the last question is, what key stakeholders are under-represented or not represented at all in the discussions that we're having?

So, I will stop. Dr. Powell will call on people to respond to these questions or to raise new questions, if you wish, and I will jump in from time to time to redirect if we're sort of getting away from the goal of this discussion.

CYNTHIA POWELL: Thank you, Dr. McCandless. We'll now open it up to questions and comments from the Committee Members first, followed by organizational representatives. Please raise your hand on the Zoom when you'd like to make comments or questions. Please remember to unmute yourself and state your first and last names to ensure proper recording. Let me just switch over. So, I'll allow Committee Members first. And Mei Baker.

MEI BAKER: Mei Baker, Committee Member. I have a question first because when Shawn, you framed this category, and first of all you talked about the timeline. Is it regarding for the nomination or general newborn screening turnaround time?

SHAWN MCCANDLESS: Great question, Mei. This is Shawn McCandless, Committee Member. Specifically, the timeline question was about the timeline from when a nomination is brought to the attention of HRSA. So, the staff works with the nominator to make sure that the nomination package is complete. The nomination package is then brought to this Committee, which refers it to the Nomination and Prioritization Work Group. The Nomination and Prioritization Work Group reviews and comes back to this Committee with a recommendation

for evidence review or not. The Evidence Review has a certainly timeline and it comes back to this Committee and data are presented or the evidence review is presented, and then this Committee votes yes or no to -- to recommend to the Secretary of HHS that the condition be added to the RUSP. And then if -- if the recommendation is that yes, it should be -- the recommendation is to add the condition, the Secretary of HHS has some period of time to respond to that and make a yes or no decision, and then it's -- and only at that point does something get added to the RUSP, and that's the timeline that we're talking about, which is quite extensive. And that doesn't even take into account the amount of time that the nominator spends preparing the nomination, collecting the data that's required.

MEI BAKER: Thank you.

CYNTHIA POWELL: Any other comments from Committee Members? Scott Shone.

SCOTT SHONE: Scott Shone, Committee Member. I think after my comments this morning, Shawn, you knew I'd have some thoughts on this and I'd love to talk more about it because I don't necessarily think that the time allotted is -- is enough to really capture a lot of this, and I thank you for bringing it up.

I mean, I think just, right off the bat, I do, as I said this morning, I feel that the system presents a lot of challenges, not just to -- based on resources, but technology and other conditions and really focuses a lot on -- on, you know, I think it holds back other potential conditions that would impact children because we focus a lot on the newborn screening, the dried blood spot, and that.

So, I think that in general, the answer to your first question would be yes, but I don't -- I think

it's beyond just resources. Resources are going to be a challenge with any pilot study or with any need to gather data and as someone who -- who said five years ago, you know, we need data to make these decisions and we need, you know, we need to identify individuals with these conditions to be able to understand what that impact is. That resources are always going to be a limiting factor, but I think it's bigger than that. And I'll also just -- I think that the multiplex is 100 percent necessary because as Dean Suhr said, the tsunami is here. I think we're -- we're there, like, I don't even think it's coming, I think we're there. And anybody who has been to any of the recent, you know, therapeutic webinars and conferences will tell you that as well. I mean, you've been there.

And so -- and finally, I'll just say that, you know, I don't know that treatment equals treatable disorder for newborn screening. I think that goes to my other comment about figuring out the timeline here. Do we have to screen for everything in -- in the -- on the dried blood spot in the newborn period or can we think about blowing up the paradigm here and really looking at ways we can look at who is under-represented and -- and look at health equity in other parts of the system beyond that every baby is born and every baby has an opportunity for newborn screening, to look at ways to identify not only some conditions that we are aware of that are more impactful later in life, but ones that we haven't even broached because we just don't have that lens on it.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Yeah. I think it's a -- I feel we cannot address every single one isolated. It's all connected. And I think if I can dare to just think without a boundary, I would say it seems to me that treatment would take major weight in the process and

other things are treated but not just medical treatment make a huge difference that can be quite important because when we -- let's think about the future. All the genetic conditions, not all, that's not all, but the majority, we can do in gene therapy and also we need to do this before symptoms occur and this is one thing we need to think about that.

The second one I am thinking is right now, let's say majority 90 percent beyond that is a genetic condition. So, Scott said it very well. Multiplex is important because of the cost in that.

And if all the genetic conditions, what's the best way one system can take it all? You have to think about the genomic, right? But genomic along cannot take this. So, in my mind, in the future, the paradigm needs to shift. So, now we use a biochemical enzyme assay taken first because it's cheap and quick and then use the molecule as a secondary like a supplemental is that in the future, we switch and start with the genomic. Then you have a biochemical enzyme assay identified who can biochemically verify them.

I know it's a lot, a lot, a lot in this simple sentiment, but I think I just want to bring this concept into this because -- I think I do feel we need to think out of the box.

CYNTHIA POWELL: Thank you.

SHAWN MCCANDLESS: This is Shawn McCandless, Committee Member. We -- we're covering a lot of ground with different questions. I'd like to -- to take a few minutes to focus on the issue of multiplexing because it sounds great in theory, but it's not obvious to me how that works. So, I'd love for someone to give me some examples of conditions that we would multiplex that where you wouldn't end up having to evaluate them separately because the issues around treatment or

testing or whatever are going to end up being different. So, Mei or Scott, you both brought up multiplexing or other people may have thoughts about that. What would be the challenges to multiplexing conditions for the review process?

CYNTHIA POWELL: Mei, did you want to comment on that?

MEI BAKER: Sure, because I was asked. I think that multiplexing is a form of technical deployment. But my concern is that the conditions would have other criteria. So, if the meeting criteria laboratory was trying to do multiplexing the best we can, I think everybody knows that the typical example is SMA. Multiplexing with SCID. You cannot ask a better, you know, example for that. But people may think lysosomal storage disorders but I would think not all the lysosomal storage disorders are created equal, and we do a lot of discussion now that we have it on the panel for MPS I and Pompe, and then we heard about Krabbe. I don't think Pompe is at the same category as Krabbe as MPS II.

So, I think that is the thing we need to think about that and also multiplexing is an indication. But I think we do well as a content profile you know, we can do a group offatty acid disorders and amino acid disorders. And if --

SHAWN MCCANDLESS: Mei, I'm just going to interrupt for a minute --

MEI BAKER: Okay.

SHAWN MCCANDLESS: -- just to redirect to say that I don't want to cause any confusion using the term multiplexing, because we're not talking today about multiplexing the tests.

MEI BAKER: Oh.

SHAWN MCCANDLESS: We're talking about considering multiple conditions at the same time for addition to the RUSP -- multiple related conditions at the same time to the RUSP. And we were using multiplexing to -- as a -- as a term to reflect that. But it's really about the way we evaluate the conditions doing more than one at a time because they're related.

MEI BAKER: Thank you, thank you. I misunderstood you. I'm glad you interrupted.

SHAWN MCCANDLESS: Well, I apologize because I was -- I was using a term that usually means something else or is used in a different context in this group.

MEI BAKER: Yeah. Well, okay. I will just have a couple seconds about this. I think I struggle with that because if they are fitting into some category or some criteria, maybe so. But if they're different, I don't know how you put a multiple disorder together, not just because they do the same testing or not, so.

CYNTHIA POWELL: Carla Cuthbert, did you have a comment?

CARLA CUTHBERT: Yeah. I'm -- yes. So, I'll just take a stab at that, Shawn. I think that that's very intriguing because again, when you say multiplexing, our minds as laboratorians go directly to the how could you get more biomarkers onto a single platform. But I do think that that's -- that still has to be part of the solution because if you're looking at perhaps a family of conditions, so perhaps a similar clinical -- clinical phenotype and perhaps a group of biomarkers that you can evaluate together that can give you information accordingly, maybe that's what you need to be able to think about. Again, we have a great

example for the amino acids and acylcarnitines. That -- that would be where I would start.

Now, we do have in our -- in our branch, I have some of my staff working on a high-resolution mass spectrometry for newborn screening to do metabolomics and again, the idea is you can only get so far with the triple clot as a platform and you do need to think outside of the box in terms of an application. So, I do still see it very linked. The testing has to go hand in hand with the clinical phenotype and you need to be able to sort of marry those together.

CYNTHIA POWELL: Thank you. Deb Freedenberg.

DEBRA FREEDENBERG: In my thinking about this, the laboratory aspects of multiplexing is not going to be the challenge. I think that will be able to be worked out even if we go to [inaudible - muffled.] But where I do have concerns on this is the treatment availability and follow-up once you start adding the availability if we talk gene therapy, if we talk genomics, if we talk whatever ERT. We're escalating exponentially the costs of the follow-up and the availability and the workforce that's out there to evaluate these children as well currently. And so, you know, I worry about equity. I worry about workforce availability, and I worry about covering the costs of the treatments that one week we had ten conditions on at the same time that all had been expensive treatments. You know, up to now, we haven't -- we had the luxury of not having to consider what it costs to treat any of these children, and hopefully it will continue to be that way. But at some point, the system's going to push back and say, you know, where is this funding coming from to treat all these kids with these really expensive treatments. And if we suddenly say, okay, we're adding twenty more conditions on, you know, in two months or whatever, I think that that's

going to be a big push on the system and I think we have to remember that newborn screening is a system and as we think about this, we need to think about the whole system, not just the laboratory component of it. We need to think about the workforce.

I mean, it's just one other thing that I just wanted to address in terms of screening at 6 months or 1 year of age.

One of the big pluses of newborn screening is it's population based, and there's a lot of concern that if we move that to 6 months or 12 months, you're not going to get the full population. You're going to have dropouts and you're not going to be able to screen the whole population, and it's just a point to consider in that if you start thinking about screening outside of the newborn screening period. So, that's just a point to consider.

But, you know, my real thought is that equity and the availability of resources if we start really multiplexing lots of conditions all at once that turn out very expensive treatments that every baby deserves.

CYNTHIA POWELL: Thank you. Mei, did you have another comment? I see your hand raised. Oh, you're muted.

MEI BAKER: No. I forgot to lower my hand. Sorry.

CYNTHIA POWELL: Okay, no problem. All right. Yeah, Shawn?

SHAWN MCCANDLESS: Yeah, maybe we could address another point that Scott raised or that came up in the questions and Scott noted. I'd just be curious to think [sic] what others think and that is the question of, is a shortcut to make the position of this Committee be that if the FDA approves a treatment for a

condition, that that -- that that is now considered a treatable condition and that there's -- that there's no need to consider anything beyond whether pre-symptomatic treatment has added benefit over symptomatic treatment? So, does FDA approval mean that it's a treatable newborn screening condition?

CYNTHIA POWELL: Jennifer or, I'm sorry, let me go to Committee Member, Kellie Kelm.

KELLIE KELM: Hi, this is Kellie Kelm from FDA. The only thing that I will raise and I know that that came up, I believe, with SMA, is that, you know, we've had instances where the therapies have been accelerated approvals, which at that point, only means that they have demonstrated a meaningful change in a surrogate endpoint and then they have post-approval studies that are required to demonstrate effectiveness. So, you know, I think we would just have to be cautious, because there are different types of FDA approval and obviously, I believe we talked about GAMT today -- no, I'm sorry, that wasn't -- that was an earlier one about, you know, also we obviously need to look at the data on -- for early treatment and again, I think there was, for example, some information on a drug label on kids under 5 and so, you know, it's hard to just say that a box is checked there, you know, but I think that you still probably have to look at the information and what that approval was for.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Yeah, and I just want to make sure, Shawn, I'm understanding correctly, because, I mean, isn't a basic tenet of newborn screening that pre-symptomatic therapy shows benefit over clinical identification? So, if -- and Kellie can speak and just did speak better than I did on this -- but that depending upon what that approval is, will drive that as well as the data that shows that -- that comparison.

So, I feel that at the heart of the question around does approval mean that it's ready to go for newborn screening, is no because there -- unless we're going to change the way that newborn screening evidence review has been done for decades now, that clear demonstration of intervening prior to symptoms benefits and that the benefits outweigh any of the risks associated with that. That's where I'm coming from with this.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Thank you. Jennifer Kwon, organizational representative for the Child Neurology Society. I appreciate Kellie and Scott speaking up. FDA approval of a drug doesn't mean that it's going to be effective or it's shown to be effective pre-symptomatically. So, I think that's really the -- that really should be the bar, that we have a treatment that has -- that has some indication -- it may not be the best evidence -- but there's some clear indication that it helps when given pre-symptomatically.

And so, I also think that it gets a little bit to the -- to the issue of equity. I feel like when we commit and accept a disease on the RUSP, in many ways, when states add that disease to their panel, they are committing to treating that disease, right? Why would you screen for it unless you are willing to treat it? But, as Debra pointed out, some of those -- the treatments seem to be getting more and more expensive. So, I think that the Committee needs to continue to be very sensitive about these individual variations and treatments and the particular disorders and that also maybe speaks to this idea of looking at multiple disorders in aggregate. What has always struck me, maybe with the exception of the fatty acid oxidation disorders, is how distinct disorders are, even like lysosomal storage disorders. They have their own

personalities and treatments and, you know, nightmare scenarios.

So, I feel, unfortunately, that part of what you're pointing out, Shawn, is how demanding it's going to be for the Committee as more and, you know, as there's a clamor for more and more rare diseases to be screened early. Thank you.

CYNTHIA POWELL: Thank you. Unfortunately, I think we need to wrap things up. Thank you so much, Dr. McCandless, for presenting this session and raising all these complex questions that are certainly very important. It's been a great discussion. Thanks to all who contributed. And I think, you know, certainly in terms of multiplexing, how the Committee, you know, can the Committee multiplex conditions that they consider, I think that's very deserving of future discussion and work.

So, this concludes day one of the August Committee meeting of the Advisory Committee of Heritable Disorders in Newborns and Children. Thank you to the Committee Members, the organizational representatives, and members of the public for attending. We will reconvene tomorrow, Friday, August 13th, at 10 a.m. Eastern time. Thank you all.

[Whereupon the meeting was adjourned.]