The Advisory Committee on Heritable Disorders in Newborns and Children

Virtual Meeting

10:00 a.m.

Thursday, May 12, 2022

Attended Via Webinar

Page 1 - 260

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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, AND COMMITTEE BUSINESS

CYNTHIA POWELL: Good morning, everyone. I will now call to order the second meeting and in 2022 of the Advisory Committee on Heritable Disorders in Newborns and Children. Welcome, I'm Dr. Cynthia Powell, Committee Chair. We'll begin by taking roll.

For Committee members, Kyle Brothers.

KYLE BROTHERS: Here.

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

CARLA CUTHBERT: I'm here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: Representing the Food and Drug Administration, Kelly Kelm. Representing Health Resources and Services Administration, Michael Warren.

MICHAEL WARREN: Here.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Present.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Here.

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

MELISSA PARISI: Here.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Here.

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

SCOTT SHONE: Here.

CYNTHIA POWELL: Next, our organizational representatives. From the American Academy of Family Physicians, Robert Ostrander. I thought I saw him earlier. Maybe we'll double check in a minute. From the American Academy of Pediatrics, Debra Freedenberg.

DEBRA FREEDENBERG: Here.

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

MAXIMILIAN MUENKE: I'm here.

CYNTHIA POWELL: From the American College of Obstetricians and Gynecologists, Steven Ralston. From the Association of Women's Health, Obstetric, and Neonatal Nurses, Katie Swinyer.

KATIE SWINYER: I'm here.

CYNTHIA POWELL: From the Child Neurology Society, Margie Ream.

MARGIE REAM: I'm here.

CYNTHIA POWELL: Department of Defense, Jacob Hogue.

JACOB HOGUE: I'm here.

CYNTHIA POWELL: And today representing Genetic Alliance, Marianna Raia.

MARIANNA RAIA: I'm here.

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

SIOBHAN DOLAN: Here.

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

CATE WALSH VOCKLEY: I'm here.

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

GERARD BERRY: Present.

CYNTHIA POWELL: Thank you. I'll now turn things over to Soohyun Kim, our acting Designated Federal Official.

SOOHYUN KIM: Thank you, Dr Powell. I will 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 receive inquiries about the ACHDNC, please let Dr. Powell and I know prior to committing to the interview or presentation.

I must also remind Committee members that you must recuse yourself from participation

in all particular matters likely to affect the financial interests of any organization with which you serve as an officer, director, trustee, or general partner unless you're also an employee of the organization or unless you have received a waiver from HHS authorizing you to participate. A-s in the case today, when a vote is scheduled or any activity is proposed, and you have a question about a potential conflict of interest, please notify me immediately. Next slide please.

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 are announced at the opening of a meeting. For this meeting, there is no public chat feature. In the Federal Register Notice we said that there would be a public comment period. Only with advanced approval of the Chair or DFO may public participants question Committee members or other presenters.

Public participants may submit

written statements. Also, public participants should be advised that Committee members are given copies of all written statements submitted by the public.

As a reminder, and as stated in the FRN, as well as the registration 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 the DFO.

If there are no further questions -- if there are no questions, I'll turn it back to Dr Powell.

CYNTHIA POWELL: Thank you, Soohyun. And before we start, I would like to say that our representative from the Agency for Healthcare Research and Quality, Kamila Mistry, is unable to join us.

Before we begin today's agenda, I'd like to take a moment to honor two monumental leaders in the newborn screening community.

We're greatly saddened by the passing of Dr. Harry Hannon and Dr. Kwaku Ohene-Frempong last week. As many of you know, Dr. Hannon has made a profound impact on the Public Health Newborn Screening System during his forty-one years of service at the CDC and beyond. He has created the Newborn Screening Quality Assurance Program at the CDC in 1978, which currently provides services to over 670 newborn screening laboratories across the US and in 88 countries. Dr. Hannon authored more than 250 scientific publications and served on over 30 national and international Committees for laboratory issues. He co-authored standards for the World Health Organization for implementing newborn screening for congenital hypothyroidism and phenylketonuria in developing and developed countries.

Over his career, he has received numerous awards and honors for his achievements, including the CDC Shephard Awards, the Robert Guthrie award, the Association of Public Health Laboratories Lifetime Achievement Award, and the

Russell J. Isler's Award in 2008. In 2008, APHL created the Harry Hannon Laboratory Improvement Award in Newborn Screening, which commemorates Harry's longstanding contributions by honoring a person working worldwide, who has made significant contributions to improving the quality of laboratory results in the newborn screening field.

And I'd like to turn things over to Dr. Carla Cuthbert CDC, a longtime colleague of Harry Hannon's.

CARLA CUTHBERT: Well, thank you, Cindy. Harry Hannon, many of you would remember him, and he was many things to many people and I'd like to just even start by just saying, for those who knew him well, for those who rubbed shoulders with him, and who had any kind of relationship with him, I am sorry for the loss that you yourself feel.

I am the Chief of the Newborn Screening and Molecular Biology Branch, and I can definitely say that the branch today, the support

that we provide, the work that we do, the vision that we are able to develop for the future to support programs, that would not exist, were it not for Harry's insight. Harry, as you know, was a very strong advocate for newborn screening and as a result of his leadership and vision at the CDC, he created what we now -- I don't want to say that we take it for granted -- but the Newborn Screening Quality Assurance Program, it has been long with us, and he did that while he was then chief of the Newborn Screening Branch.

This program, as Cindy has indicated, started off incredibly small and it's grown to cover about 700 participating programs in about 88 countries.

And at his funeral yesterday, if you've had an opportunity to listen in, the pastor said that Harry had done enough in his life and then he was called home. And so, I appreciate a moment to be able to honor Harry, and I do recognize that he's left an amazing legacy behind. And while we're very profoundly

sad that he's no longer with us, we know that we are part of his legacy and that it is on his shoulders that we continue to create new programs, resources, and to support the newborn screening community, both domestic and international. So, thank you.

CYNTHIA POWELL: Thank you, Carla. Dr. Kwaku Ohene-Frempong dedicated his life and career to working with sickle cell disease and patients with this condition. Born in Ghana, his record of excellence as a student athlete earned him a scholarship to Yale to study pre-med and he received his medical degree from the Yale School of Medicine. While finishing his degree, his son became the first baby diagnosed with sickle cell disease by Dr. Howard Pearson in the pioneering Newborn Screening Program at Yale in 1972. His first-hand experience with sickle cell and newborn testing motivated him to dedicate his life and career to studying and advocating for sickle cell.

Dr. Ohene-Frempong was the leading

pediatric sickle cell physician, he was Director Emeritus of the Comprehensive Sickle Cell Center at the Children's Hospital of Philadelphia, Emeritus Professor of Pediatrics at the Pearlman Center of Medicine at the University of Pennsylvania, and President of the Sickle Cell Foundation of Ghana. He pioneered a newborn screening and follow up program in Ghana, where 1 in 50 babies has sickle cell disease. This has been a training center for sickle cell care and research in Africa.

Dr. Ohene-Frempong also founded the Sickle Cell Foundation of Ghana and was a founding member of the Global Sickle Cell Disease Network.

Dr. Hannon and Dr. Ohene-Frempong will be greatly missed. Please join me in a moment of silence to honor them. Thank you. May I have the next slide please.

I also would like to take some time to acknowledge that this will be the last Advisory Committee meeting for Dr. Scott Shone

and myself, whose terms will end in June. Dr. Shone, on behalf of HRSA and the Advisory Committee, we thank you for your outstanding service and contributions to the Committee and the field of newborn screening. You have dedicated countless hours to attend Committee meetings, contributed to Committee products, participated on the Nomination and Priority and Lab Standards and Procedures workgroups, and applied your in-depth subject matter expertise to Committee deliberations and decisions. As a token of our gratitude, we have sent an appreciation plaque to Dr. Shone ahead of the meeting. If you have it there, you can show it; if not, that's okay. Also – there it is. Also, we will be sending a certificate and letter of appreciation from the HRSA Administrator, Carole Johnson. I would now like to open the floor to Dr. Shone to say a few words.

SCOTT SHONE: Thanks, Dr. Powell. It's always dangerous when you let me have an open mic, but. Serving on this Committee has

been just an absolute honor and really, I was talking to my wife last night, it was a career bucket list item that I achieved way earlier than I ever anticipated.

I'd just like to say that, you know, when I started in newborn screening, my training is in microbiology and immunology, and I was in bioterrorism and finding it not rewarding and took an opportunity to move to newborn screening, where I found something that I'm incredibly passionate about. But, I always tell the story of when I started in New Jersey, the program there was having some challenges and they had just bought three new tandem mass spectrometers and the Assistant Secretary said to me, okay, we have three new mass specs. You need to validate them as your first job, and I said okay great. What's a mass spec and how do you validate it? And that was my introduction to newborn screening.

The good news was that three weeks later, the department had already requested an

external review of the New Jersey program and in walked Gary Hoffman from Wisconsin, Brad Thereau from the NFGRC and Harry. And Harry was a tireless advocate and mentor, and I miss him terribly. So, it has been an honor to serve on this Committee and contribute to the system.

My service is not done. I don't retire for decades. So, you're all going to have to listen to me for a lot longer. So, thank you everybody. Thank you, Dr Powell, for a few moments and I wish my fellow Committee members luck, because I hate to leave when the challenges just continue to crescendo. But I'm always here rooting for you all and would be happy to serve in any role that you see I can fit in the future. Thanks.

CYNTHIA POWELL: Thank you, Dr. Shone. Once again, for your service. You have made and continue to have a lasting impact on newborns and their families across the nation.

For our first item of Committee business, I'd like to announce that Dr. Margie

Ream will replace Dr. Jennifer Kwon, who is now serving as a Committee member, as the organizational representative for the Child Neurology Society.

Margie Ream is an Assistant Professor and Child Neurologist in the Department of Pediatrics at Nationwide Children's Hospital at the Ohio State University College of Medicine. She has an extensive research background in fetal physiology and nervous system development, and this was the focus of her PhD thesis work. She has public policy experience and subject matter expertise regarding leukodystrophies and other rare genetic diseases as Director of the Leukodystrophy Clinic at Nationwide Children's Hospital.

She's a member of the Ohio Newborn Screening Advisory Council, a member of the Secretary's Advisory Committee for Heritable Disorders in Newborns and Children's Follow-up and Treatment Workgroup and a co-investigator for the HRSA Evidence Review Group.

As the provider of nearly all fetal neurology consultations at Nationwide Children's Hospital, Dr. Ream also has extensive contact with maternal fetal medicine specialists and neonatologists as they identify and develop postnatal treatment plans for infants with prenatal and neonatal diagnoses of genetic and metabolic brain disorders.

Dr. Ream, we are excited to welcome you. Next slide.

At the February 2022 meeting, the Committee voted in favor of recommending adding MPS II to the RUSP. Following the meeting, I have sent a letter to Secretary Becerra with the recommendation from the Advisory Committee. Committee members and organizational representatives received a copy of the letter in the briefing book and for the public, a copy has been posted on the Committee's website. Please remember that the Secretary makes the final decision on whether or not to accept the Committee's recommendation. This decision will

be posted on the Committee's website once it's available.

As I mentioned at the February Advisory Committee meeting in October of 2021, the National CMV Foundation submitted a RUSP nomination package for congenital cytomegalovirus newborn screening. The Nomination and Prioritization Workgroup is reviewing the nomination package for congenital cytomegalovirus and will keep both the nominators and the rest of the Committee informed of next steps. Next slide.

As announced at the February meeting, Federal Register Notices have been published, calling for nominations for new voting members and new organizational representatives. Both of those just closed and the nominations are currently under review. We will be reviewing the nominations for the voting members to ensure that the membership of the ACHDNC is fairly balanced in terms of points of view represented and that it meets the requirements as outlined in the

Newborn Screening Saves Lives Act, which include medical, technical, or scientific professionals with special expertise in the field of heritable disorders, or in providing screening, counseling, testing, or specialty services for newborns and children with or at risk for having heritable disorders. Also, individuals who have expertise and ethics, infectious disease, and who have worked and published material in newborn screening, and members of the public, having demonstrated expertise or lived experience. Thank you to everyone who has submitted the nominations.

Regarding capacity and prioritization, the Committee had an initial discussion at the February meeting on its capacity to review multiple nominations per year. I had mentioned that I intend to form a workgroup comprised of current and former Committee members and other subject matter experts to develop criteria and a process for prioritizing the review of nominated conditions.

This work is currently in the contracting phase, and we expect the work in this area to begin in 2022. This will be further discussed at an upcoming Committee meeting. Next slide please.

Thank you, Committee members and organizational representatives, for reviewing the February 2022 meeting summary. Are there any other corrections to the meeting summary before we vote? Is there a motion to vote on whether or not to approve the February 2022 ACHDNC meeting summary?

KYLE BROTHERS: This is Kyle Brothers, so moved.

CYNTHIA POWELL: Is there a second?

SHAWN MCCANDLESS: This is Shawn McCandless, I second.

CYNTHIA POWELL: Is there any discussion of the motion? Hearing none, Committee members, when I call your name, please state, yes, if you're in favor of approving the February meeting summary, no, if you are not in

favor of approving the summary, or you may also abstain. As I mentioned earlier, Kamila Mistry from Agency for Healthcare Research and Quality is not able to attend this meeting. We'll go next to Kyle Brothers.

KYLE BROTHERS: Yes.

CYNTHIA POWELL: From the Center for Disease Control and Prevention, Carla Cuthbert.

CARLA CUTHBERT: Yes.

CYNTHIS POWELL: Jane DeLuca.

JANE DELUCA: Yes.

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

KELLIE KELM: Yes.

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

MICHAEL WARREN: Yes.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Yes.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Yes.

CYNTHIA POWELL: From the NIH, Melissa Parisi.

MELISSA PARISI: Yes.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Yes.

CYNTHIA POWELL: Cynthia Powell, I vote yes, and Scott Shone.

SCOTT SHONE: Yes.

CYNTHIA POWELL: Thank you. The February 2022 ACHDNC meeting summary has been approved. Thank you, Committee members. May I have the next slide, please.

So, the Committee will meet today, May 12th and tomorrow, May 13th. Here are the meeting topics for today. First, we will have an expert panel presenting on updates on homocystinuria newborn screening. Next, we will have the first public comment session of the meeting, where we will hear from seven individuals, including Danae Bartke from HCU Network America, Terri Klein from the National

MPS Society, Dylan Simon from EveryLife Foundation for Rare Diseases, Dean Suhr from MLD Foundation, Kim Stephens from Project Alive. We will also hear from Kim Tuminello and Heidi Wallis, who have registered to provide public comments on the Committee vote on guanidinoacetate methyltransferase or GAMT deficiency.

Then, the Evidence-Based review Group will provide an overview of the Evidence-Based review for GAMT deficiency.

Afterwards, Committee liaisons to the Evidence Review Group, Dr. Jane DeLuca and Dr. Shawn McCandless will present the Committee report on newborn screening for GAMT deficiency.

At approximately 2:50, the Committee is scheduled to begin the vote on whether or not to recommend GAMT deficiency for inclusion on the Recommended Uniform Screening Panel. We will end today at 3:20 Eastern time and reconvene tomorrow morning at 10:00 a.m. Next slide, please.

Tomorrow, Friday, May 13th, the

Committee will begin with the second public comment period, where we will hear from Nikki Armstrong from Parent Project Muscular Dystrophy, Richard Poulin from Special Education Teaching and Learning, Inc., and five individuals who will provide public comments on the Committee vote on Krabbe Disease, including Jackie Wagner, Natasha Spencer, Carlita Blackwell, Joanne Kurtzberg, and Dieter Matern.

Following the public comment period, the Nomination and Prioritization Workgroup will provide a summary of the nomination package for Krabbe Disease.

Immediately after the Nomination and Prioritization Workgroup presentation, the Committee will have an opportunity to discuss the nomination package and hold a vote on whether or not to move Krabbe Disease forward to full Evidence-Based review.

The last session tomorrow will be a presentation from the Newborn Screening Family Education Program. We will aim to adjourn the

meeting at approximately 12:40 p.m. Eastern time.

Now, I'll turn things back over to Soohyun.

SOOHYUN KIM: Thank you. For the record, Susan Tanksley from Association of Public Health Laboratories and Robert Ostrander from American Academy of Family Physicians are present.

For members of the public, audio will come through your computer speakers. So, please make sure that you have your speakers turned on. If you cannot access the audio through your computer, you may dial into the meeting using the telephone number in the e-mail with your Zoom link.

As mentioned previously, this meeting will not have an all-attendee chat feature. But we do have the public comment period scheduled later today.

Committee members and org reps, audio will come from your computer speakers and you'll be able to speak using your computer

microphone. If you cannot access the audio or microphone through your computer, you may dial in to the meeting using the telephone number in the e-mail with your user-specific Zoom link.

Please remember to speak clearly and remember to state your first and last name to ensure proper recording for the Committee transcript and minutes.

The Chair will call on Committee members and then organizational representatives. In order to better facilitate the discussion, we remind you to use the raise hand feature when you would like to make comments 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 feature may be in a different location. To troubleshoot, please consult the webinar instructions page in your briefing book. Next slide, please.

To enable closed captioning, please

select the closed captioning icon from your Zoom Taskbar and then select show title from the menu that appears.

Thank you. Back to Dr. Powell.

CYNTHIA POWELL: Thank you, Soohyun. In 2019, the Committee received public comments from the homocystinuria or HCU Network America about the low sensitivity of newborn screening for homocystinuria. They estimated at the time that up to 50% of cases may be missed, and the Committee discussed following up on how to address this issue.

I have invited three speakers today to provide us with an overview of the current status of HCU newborn screening and updates, possible solutions to the challenges with HCU screening, and any advances in the screening technology.

Our first presenter is Dr. Marzia Pasquali, who will provide us with an overview of the Status of Newborn Screening for Homocystinuria. Dr. Pasquali is a Professor of

Pathology, the Program Director of the Accreditation Council for Graduate Medical Education Accredited Fellowship Program in Clinical Biochemical Genetics at the University of Utah School of Medicine, and the Section Chief and Medical Director of Biochemical Genetics at ARUP Laboratories.

Dr. Pasquali earned her degrees of Doctor in Pharmaceutical Chemistry and Technology and Pharmacy Doctor at the University of Parma School of Pharmacy in Italy. She trained in Clinical Biochemical Genetics at Emory University in Atlanta Georgia, where she later served as the Co-Director of the Biochemical Genetics Laboratory. Dr. Pasquali is Board Certified in Clinical Biochemical Genetics. She is a member of the Society for Inherited Metabolic Disorders, the American College of Medical Genetics and Genomics, and several other professional societies. Her research interests are newborn screening disorders of carnitine and creatine metabolism and transport and lysosomal storage

disorders. I'll now turn things over to Dr. Pasquali.

UPDATES ON HOMOCYSTINURIA NBS STATUS: PANEL PRESENTATION

MARZIA PASQUALI: Thank you, Dr. Powell for the introduction. Today, I will talk about homocystinuria. Next slide.

I will give a brief introduction of homocystinuria and the biochemical patterns, a clinical description of classic homocystinuria, and then I will briefly introduce a newborn screening and how it's currently done. Next slide.

Homocystinurias are a group of disorders characterized by elevated homocysteine and often elevated homocystine. The difference in between homocysteine and homocystine is that homocystine is formed by attaching to homocysteine molecules. Only 1 to 2% of total homocysteine is present as such. The rest is bound to proteins through a disulfide bond or is present as a homodimer, free homocystine. Again,

you can see that there are two molecules of homocysteine that are bound together.

When we look at plasma amino acid analysis, what we are measuring, we are measuring this dimer, the free homocystine, which account for only about 10% of the total homocysteine.

If you want to measure total homocysteine, you need an additional step and additional chemical reaction that reduces the -- reduces the bond and breaks this bond and breaks this dimer into the two homocysteine molecules. Next slide.

This slide shows the metabolic pathways for sulferamino acid. We can see three -- the three major pathways, re-methylation, transfer of the methyl group, and trans-sulfuration. If we start from the methionine, there is a series of enzymatic reaction that are transferring the methyl group to other molecules such as guanidinoacetate to synthesize the creatine of glycine to synthesize the sarcosine and form -- this series of reaction, methionine

is converted to homocysteine. Homocysteine is then converted to cystathionine by the action of the enzyme cystathionine beta synthase, which uses B6 vitamin, B6 pyridoxine. Then, homocysteine is remethylated to form methionine again by a series of reaction and co-factor including vitamin B12 to again going back to methionine.

In disorders of homocysteine remethylation, those that are on the left of the screen in the green box, the characteristic marker would be elevated total homocysteine, elevated homocystine, and the low methionine because again, the remethylation of homocysteine to methionine is impaired.

In disorder of the methyl group of transfer, we are going to see markedly elevated methionine with either normal or mildly elevated homocysteine and normal homocystine. In the cystathionine beta synthase deficiency, which is in the blue box at the bottom, we are going to see markedly elevated methionine, elevated --

markedly elevated sulfa homocysteine and elevated homocystine as well. Next slide.

So, there are mainly four biochemical markers that are necessary for the diagnosis of homocystinuria. Methionine, which is elevated in cystathionine beta synthase deficiency and low in disorder of homocysteine remethylation.

Total homocysteine and free homocystine, which are elevated in both disorders of remethylation and in cystathionine beta synthase deficiency.

And then, we also have a methylmalonic acid, which is elevated in disorder of vitamin B12 metabolism, which impairs homocysteine remethylation and methylmalonic acid metabolism. Next slide.

So, let's talk now about classic homocystinuria. Classic homocystinuria is caused by deficiency in cystathionine beta synthase, which is an enzyme requiring vitamin B6 and is also in elevated methionine and elevated

homocysteine and the homocystine.

The incidence calculated by newborn screening, this is a paper published in 2014 looking at ten years of newborn screening. The incidence was 1 in 456,000 newborns. The estimated prevalence is 1 in 200,000 to 1 in 335,000. This indicates that newborn screening can miss cases of classic homocystinuria.

Classic homocystinuria is inherited as an autosomal recessive trait.

The diagnosis is accomplished through newborn screening and currently the marker -- the primary marker is elevated methionine. Plasma amino acids will show elevated methionine and presence of free homocystine, total plasma homocysteine is usually markedly elevated, and usually is even greater than 100 µM with the normal range less than 12.

The diagnosis is confirmed by DNA sequencing.

The therapies start with a low-protein diet with amino acid mixture that does

not contain methionine, pyridoxine in responsive patients, betaine to favor homocysteine remethylation, and methyl folate and vitamin B12, which will help again in the remethylation processing. Next slide.

What is the clinical presentation of classic homocystinuria? We have manifestation to the eyes and patients show lens dislocation and/or severe myopia. Skeletal systems is involved as well and these patients usually have tall stature with long limbs, longer arms and legs, scoliosis, and osteoporosis. Thromboembolism is a characteristic of this condition and developmental delay and intellect disability. Thromboembolism is the major cause of early death and morbidity in patients who are not treated and it's manifesting in late childhood and young adults, which is not the age group which typically can absorb thromboembolism, thrombotic disorders.

There is a milder phenotype, which is B6-responsive homocystinuria. The majority of

infants identified by newborn screening currently are B6-non-responsive and this is because it's rare for a B6-responsive patient to have the methionine elevated and when I say methionine elevated, I mean methionine above the decision limit or the cutoff that has been established by the newborn screening lab. So, it's rare for a B6-responsive infant to have methionine elevated at the time of the first newborn screen, which is collected between 24 and 48 hours of life.

Complications of homocystinuria can be prevented by early identification and treatment. Therefore, newborn screening -- sensitive newborn screening program is necessary. Next slide.

How is newborn screening done currently. Well, we all know tandem mass spectrometry is universally used and the sensitivity of the newborn screening for homocystinuria depends upon the choice of the markers and the choice of decision limits. Methionine is the primary marker and again may

not be above the cut-off in classic homocystinuria especially for the B6-responsive variant. Therefore, classic homocystinuria may be missed.

Ratios can be used as secondary markers to increase the sensitivity and one example of the ratios could be Met/Phe ratio. Next slide.

Other causes of -- there are other causes of elevated methionine in newborn screening which increase the noise of the screening. These are high-protein diets. It's not very common but in our experience, we have seen infants with elevated methionine on newborn screening because they were fed a high-protein diet. Low birth weights and prematurity, again, in our experience, one third of the infants with elevated methionine were premature. Liver disease, deficiency of the enzymes which are involved in the transfer of the metal group will result in elevated methionine and then citrin deficiency, also known as citrin anemia type 2

and tyrosinemia type 1, are conditions that can result in elevated methionine. Next slide.

So, how do we reduce the noise. We can use a second-tier test. Second-tier tests are tests that are run on the same sample used for the primary screen. So, there is no need to re-collect the sample, but targeting different analytes. And the purpose again is to identify infants at risk to have a metabolic disease while reducing the false positive and also reducing the false negatives. Next slide.

What is the strategy for second-tier tests. Because the noise is introduced by the fact that the marker of the specific condition may be elevated also due to different causes, so the strategy would be to identify specific markers for the condition. In cases of homocystinuria, the specific marker would be total homocysteine.

There are also molecular second-tier tests, but in this case, biochemical second-tier test is going to be much more effective. Dr.

Matern and Dr. Petritis are going to talk about second-tier tests and their effectiveness. Next slide.

I'm just going to end my presentation with a summary of the recommendation for newborn screening for homocystinuria that were published three years ago in the *Journal of Inherited Metabolic Disorder*s and the recommendation where to revise the decision limits with reference to the median, use a combination of markers, so like methionine and/or a ratio Met/Phe, use post-analytical tools, again, which will help reduce the noise, and implementation of second-tier tests. Next slide.

In summary, newborn screening for classic homocystinuria is possible and can be effective. The primary marker currently used is not sensitive to detect all cases and we need more sensitive and specific markers.

Multiple markers increase the sensitivity of the screening.

Second-tier tests are effective in

reducing the number of false positives and false negatives, but they can be a burden to newborn screening laboratories.

The use of bioinformatic tools can help identifying samples needing the second-tier tests and decreasing the burden to newborn screening laboratories. Thank you.

CYNTHIA POWELL: Thank you, Dr Pasquali.

The Committee will hold questions and comments until after all panelists have presented.

Next, I would like to welcome Dr. Dietrich Matern, who will discuss the possible and available solutions to the HCU newborn screening problem. Dr. Matern is a Professor of Laboratory Medicine, Medical Genetics and Pediatrics and Co-Director of the Biochemical Genetics Laboratory at the Mayo Clinic in Rochester, Minnesota.

Dr. Matern's research activities involve the development and improvement of

laboratory assays for the effective and efficient screening diagnosis and follow-up of patients with inborn errors of metabolism.

He has also participated in the laboratory evaluation of animal models and clinical trials as a collaborator with colleagues at Mayo Clinic and other academic institutions.

He authored or co-authored more than 160 peer-reviewed publications and textbook chapters.

Dr. Matern currently serves on several committees, boards, and working groups of the Minnesota Department of Health, the American College of Medical Genetics and Genomics, the College of American Pathologists, the Association of Public Health Laboratories, the Clinical Laboratory Standards Institute, and patient advocacy organizations.

From 2011 to 2018, he served as a Member of this Committee, the Advisory Committee on Heritable Disorders in Newborns and Children.

I'd like to turn it over now to Dr.

Matern.

DIETRICH MATERN: Thank you, Dr Powell. Can you hear me?

CYNTHIA POWELL: Yes.

DIETRICH MATERN: Okay, thank you. Thank you for that very kind introduction and for inviting me back to the Committee and talk to you about homocystinuria's newborn screening problem, and what are possible and available solutions. Next slide, please.

So, as you heard before, methionine is easy to measure. Everyone uses tandem mass spectrometry to do so, but it is not sensitive, even with a low cut off. And, as this graph shows, it's also not very specific, because there is a significant overlap between methionine values in babies treated with total parental nutrition and those that have homocystinuria.

I was made aware of the issue in 1999 when Harvey Levy and others published this paper in *The New England Journal of Medicine*, pointing out that there's a significant problem

of missing babies with homocystinuria when using the methionine as the primary marker. Next slide.

Also, in 2007 when tandem mass spectrometry was introduced into newborn screening programs, this Dutch group pointed out the problem of TPN and some TPN solutions that included a lot of methionine-causing problems with screening for homocystinuria. Next slide, please.

As Dr. Pasquali already mentioned, a proposed solution has been made that you might want to just add a ratio, such as methionine phenylalanine, which is again, easy to measure when you use tandem mass spec and you get both values from methionine phenylalanine, but the problem here is again that it is not sufficiently sensitive and also not specific, as you can see, in that graph TPN again overlaps quite a bit with patients with homocysteine just for the methionine to phenylalanine ratio. Next slide, please.

As also was mentioned, molecular testing is often thrown into the mix as solving the newborn screenings, but if you look, just a few days ago in ClinVar, 974 variants in the CBS gene are listed there, and of those, only 27% of known significance, which means that the rest, 714 variants currently, we don't really know exactly what they might be doing. So, if you actually have a genotype, the chances that you have a not-so-certain variant included in the genotype it's quite high. Next slide, please.

The other proposed solution, which you will hear in the next talk, is to just measure total homocysteine as a primary screen replacing basically methionine and that would probably work very well, as you can see here, because patients with homocystinuria, as you just heard and also before, have really high total homocysteine. Next slide, please.

Dr. Petritis and Carla Cuthbert and others at the CDC published a feasibility study using a new technology to do so -- next slide,

please -- but I think what Dr. Petritis will tell you, this is not quite ready for prime time. Next slide, please.

But there is currently a solution available, and that is to major total homocysteine as part of a second-tier test. It's sensitive, it requires additional technology in the laboratory, liquid chromatography, tandem mass spectrometry, but it can be regionalized. So, not every screening program has to do this because homocystinuria, as you know, is not a time-critical condition. So, sending a specimen overnight to another laboratory to do the testing is not a problem and for homocystinuria, you could even batch the analysis of doing it only twice a week or so, and you can add additional markers.

So, when we published this for the first time in 2010, we actually developed an assay where we measured total homocysteine, methylmalonic acid, and 2-methylcitric acid to support newborn screening for homocystinuria and

other conditions. This test is not unique to Mayo Clinic, so not -- you don't have to be the Mayo Clinic to do this test, as published only last year, Spain implemented the test and in between, there were other papers doing the same. Next slide, please.

So, when would you use this test. Again, if you include more than total homocysteine, such as methylmalonic acid and 2-methylcitric acid, you can use it actually when you have elevations of C3-acylcarnitine to differentiate between false positives and propionic acidemia and methylmalonic acidemias when methionine is elevated but also when methionine is reduced -- next slide -- because there are remethylation disorders that also deserve identification for newborn screening, because, as in this paper, it was shown these conditions are treatable, but the patients benefit when this treatment is initiated early, making a case for newborn screening.

So, overall, about 1% to 2% would

deserve the second-tier test or require the second-tier test based on a high C3-acylcarnitine or high or low methionine. Next slide, please.

We published recently our experience with the second-tier test and, as you can see in that table, there are multiple conditions that are indicated by high C3 or high or low methionine that can be better determined using the second-tier test and most importantly, you can reduce false positives and exclude total parental nutrition. Next slide, please.

We have done this now between 2012 and 2019. In that timeframe, more than 5,600 times and, as you can see, we found 44 babies which had an isolated homocysteine elevation. So, these patients had homocystinuria. Next slide.

What's a second-tier test? So, in my opinion, it's a cost-effective approach to reduce false positive results in cases like homocystinuria where you have the problem of overlap with a poorly specific insensitive

marker. You do it after the primary screen. You don't ask for another specimen. No additional patient contact. You use the original newborn screening blood spot, and then if the second-tier test is normal, it overrules the primary screen. That's how to reduce false positives and there's plenty of examples out there where this is being done biochemically, but the best known is probably by molecular and CF screening. Next slide, please.

So, what happens at the birth place, a sample is collected. Next slide.

The specimen goes to the screening lab. They do their primary screen, and, in most instances, everything is fine and everyone is happy. Next click.

However, if it's abnormal, often a repeat is requested, the testing is done again. It could be abnormal again, and then you finally get to confirmatory testing. I don't think that's a good idea. It wastes time, it wastes effort, it creates anxiety in the families, and a

lot of work for the follow-up people. Next slide, please.

So, when you have a second-tier test, you take another punch. You do that, and in most instances, it's normal, everyone should be happy.

If it is abnormal -- next slide -- then, you go right to confirmatory testing and the physician can tell the family with good confidence that this is most likely a true positive result and requires action. Next slide, please.

So, when we did newborn screening using tandem mass spec for the state of Minnesota in the timeframe from April 2005 when we started using our second-tier tests through December 2011, if we had not used the second-tier test but applied the same rules to use the second-tier test, we would have had 10,900 false positives among half a million babies, which is 2% and the follow-up cost calculated based on 2012 cost data and using the ACMG algorithm to determine what

kind of work is required to follow up on an abnormal screening result, it would have cost the state $9.3 million. However, we did have a second-tier test -- next slide, please -- and with the second-tier test, we had 31 false positives and a follow-up cost of $400,000 and basically could save almost $9 million to the health care system in Minnesota. Next slide, please.

If we extrapolate this to 4 million babies born in the US, the false positives again would be 2.2%. The total follow-up costs, based on the 2012 data -- so not based on 2022 data where it would be likely much higher -- would be $74 million. Next slide, please.

With a second-tier test, if it was applied across the US, we could save $71 million in 2012, probably $100 million today, in health care costs. Next slide, please.

So, in summary, newborn screening for homocystinuria is currently hampered by the marker methionine. There is a solution currently

available using the second-tier test. It's efficient, effective, and it is accessible, and it can identify most cases of homocystinuria if we really wanted to do this.

Every state says we're screening for homocystinuria, but are we really? Total homocysteine may be added and a new screening essay in the future, and you will hear about that and I think it's also, as I hope to have showed you, we could reduce unnecessary health care spending if we really considered newborn screening as a system and not compartmentalized.

The issues that we often hear is why screening labs do not want to use a second-tier test that is done outside or even inside their own walls, is because they don't have the funding to do the testing in-house and they don't have the permission to send out samples or create additional costs by sending it because people do not look at newborn screening as a system and that we can save for the overall health care system, and not just for single laboratory. Next

slide.

With that, I am done and I really would like to acknowledge everyone in my laboratory and specifically our genetic counselors and my colleagues running the laboratory, and I will be happy to answer any questions later.

CYNTHIA POWELL: Thank you, Dr. Matern.

Our last panelist is Dr. Kostas Petritis, who will give us an update on advances in HCU newborn screening detection.

Dr. Petritis received his Master of Science and PhD degrees in Analytical Chemistry from the University of Orléans France. In 2002, he joined Pacific Northwest National Laboratory in Richland, Washington as a postdoctoral fellow and later as a senior staff scientist, where he worked in the field of mass spectrometry-based proteomics.

In 2009, Dr. Petritis was hired as an Associate Professor and Laboratory Head of the

Translational Genomic Research Institute in Phoenix, Arizona to work on biomarker development.

In 2014, he joined the Arizona Office of Newborn Screening and Phoenix Children's Hospital as a principal investigator, where he led several federal public health and research grants before joining the CDC in June of 2017.

He has worked on bioanalytical mass spectrometry, biomarker development, automation, predictive algorithms, and proteomics research.

His current interests include, but are not limited to, advanced analytical methods, development and validation for newborn screening, development of dried blood spot space quality assurance materials and calibrators, clinical assays, harmonization, and metabolomics. He has co-authored more than 200 communications.

I'll now turn things over to Dr. Petritis.

KOSTAS PETRITIS: Thank you for the

kind introduction. Next slide, please.

So, this is the outline of my presentation, for today. I will start by presenting a slide on current analytical practices for homocystinuria screening in newborns, following for describing some work towards a universal second-tier screening assay for biochemical newborn screening biomarkers, including homocysteine. And then, I will describe some proof of concept work that we did on combining first- and second-tier screen biomarker using separation before analysis by the tandem mass spectrometry. And finally, finally, the majority of my presentation will focus on our efforts towards multiplexing homocysteine detection in primary flow-injection analyses tandem mass spectrometry screening. Next slide, please.

So, as you heard already twice, methionine is currently used as a biomarker in primary newborn screening for homocystinuria. Unfortunately, it has poor sensitivity and

specificity.

Total homocysteine is the most specific marker for homocystinuria, but currently, it's only used as a second-tier screening marker following a presumptive positive methionine elevation in primary screening.

Now, as Dr. Matern and Dr. Pasquali told you, there are second-tier screening methods out there either for only total homocysteine or multiplexing mainly with organic acids.

Now, generally speaking, I want to mention that second-tier screening assays are very fragmented. Many of them, it's just the one assay for one disease. You have like one second-tier screening assay for muscular dystrophy, one for Krabbe disease, one for MPS I, one for congenital adrenal hyperplasia, and I feel this is one of the reasons that can lead to low adoption rates for in-house second-tier screening. So, too many assays to maintain.

Some other agencies said that some of the assays have relativity low reflex rates.

So, you may have only, you know, one specimen to analyze per week and you still have to maintain the method, make standards, calibrate the decisions before you run one specimen or two.

Other reasons that have been mentioned is the need to have a separate mass spectrometry instrument and delays in reporting.

As Mr. Matern mentioned, regional second-tier scanning is a possibility. Next slide, please.

So, in order to overcome some of those limitations, we ask ourselves, can we just take all of those second-tier screen biomarkers and just make one assay and be able to analyze all of them.

And we also saw an opportunity with the introduction of adrenoleukodystrophy in the Recommended Uniform Screening Panel because, as you know, adrenoleukodystrophy is using mainly flow-injection analysis with the mass spectrometry to analyze lysophosphatidylcholines, LCP-26, and there are like a lot of high

correspondents that require second-tier screening.

So, some states reflex up to 3% of their daily specimens to second-tier screening for ALD.

So, the idea was like, okay, let's take LPC-26 and try to multiplex with all the other biomarkers for diseases that have no reflex rate and come up with an assay that can generate actually enough specimens every day in the laboratory to justify to do second-tier screening in-house daily. And this is what we came up with.

So, we have a method. It multiplexes about 19 second-tier screening biomarkers, including homocysteine -- that's circled here in red -- and LPC-26, organic acids, LPC, leucine, isomers, and other analytes of interest.

So, in order to achieve that, we use hydrophilic interaction chromatography coupled with mass spectrometry and we can validate this

assay in-house.

We have the manuscript. It's currently in clearance and it will be soon submitted for analytical chemistry. Next slide, please.

As Dr. Matern said, we also did some proof of concept work where we said, well, let's try actually to go combine first- and second-tier screening analytes and using separation before mass spectrometry, and for this work, we use the electrophoretic separations that are like extremely fast. You can see from the figure -- I don't know if you can see it -- but this window here is 0.8 to 1.4 minutes, so very high peak capacities. You can do acylcarnitines, you can the amino acids, and at the same time, you can do your second-tier screening analytes, Hcy that is shown here in red, and you can even achieve a baseline separation for very difficult analytes like leucine, isoleucine, and alloisoleucine. So, biomarker for L-isoleucine.

There are some limitations. There

is an inability to analyze organic acids, which is inherent to this method, we couldn't do it the same, and some other cycle-times considerations. All of those limitations are described into our recently published paper in *Clinical Chemistry* in December of 2021.

But, as Dr. Matern said, this particular assay is not ready for prime time, but it shows kind of what you can do currently with separation before mass spectrometry analysis. Next slide, please.

So, I will transition now talking for the main topic of my presentation, which is actually multiplexing total homocysteine into primary flow-injection mass spectrometer.

So, as we said, one of the complications and challenges is that the reducing step is required to be able to quantify total homocysteine. That's because more than 98% of homocysteine is either oxidized with itself or it's bound to proteins. So, we needed a reducing agent to be able to cleave the disulfide

bone and make total homocysteine detection feasible.

So, when we started this work, you know, we had no idea of the challenges that we were going to face. There was nothing published in the literature, of course. So, you know, we had no idea, you know, are they going to be interferences with total homocysteine during flow-injection analysis and mass spectrometry? What's going to be the impact of reducing agents on other biomarkers? Are there some solvent extraction issues or workflow considerations? We needed to respond to all of that. Next slide, please.

So, if you look at the literature, there are currently two common disulfide bond reducing agents. One is DTT and the other is TCEP. DTT, and I show the structures here, has actually two free thiol groups, which is important for something that we see later, TCEP doesn't. So, DTT is the most commonly used in newborn screening papers. It's a reversible

reaction, the reduction that you can get with DDT, and does not ionize in positive mode mass spectrometry, which is good.

On the other hand, TCEP is a stronger reducing agent, has better stability. It has been important that it can form byproducts with heating, it does ionize in positive ion mode mass spectrometry, and we saw some interesting research paper where there is actually potential for post-reaction removal if you bind the TCEP with magnetic nanoparticles. So, you can do the reaction and then eliminate the TCEP from your solution. Next slide, please.

So, first of all, we want to see if there are any identification of any -- any interference with the homocysteine. We thought that maybe we would be lucky, and there would be none. So, in order to see if there are any, we took just a specimen rich with homocysteine. We did our sample prep on test one and we looked at high-resolution mass spectrometry to be able to see if there are any interference of the

transition 136 to 90, which is what we use for total homocysteine. And you can see that they were like definitely several interferences and we identified the major ones, which actually were coming from us using internal standards that interfere with total homocysteine transition. So, one of them is methionine D3. D3 stands for deuterium, which substitutes hydrogen. The mass for this one has less than 153 but it fragments to create another amnion at 136, which is a paradigm homocysteine and then the fragmentation is the same with leucine, you can see it here. The M+1 ion interferes with homocysteine transition. And then there are some other minor interferences.

So, this is actually all those different items that you can see here with high-resolution mass spectrometry, you wouldn't -- they will all come under one peak because of the resolution of triple quads that are using newborn screening.

So, we had to come up with another

way to solve this problem, and then we thought that maybe we should try specific thiol derivatization to see if the total homocysteine -- - the homocysteine transition from 136 to something higher that hopefully is not going to interfere with other compounds.

Now, just a reminder that homocysteine currently is the only newborn screening biomarker that has free thiol, so if we do thiol derivatization, homocysteine will be the only compound that it's affecting. Next slide, please.

So, we tried several times with derivatization agents and we ended up using N-ethylmaleimide, which I will refer to it as NEM from now on. So, NEM, we add to any free thiol group. That includes, of course, homocysteine, but DTT as well because, as you remember, we had -- it has two free thiol groups. NEM shifts the homocysteine transition from 156 to 90 to 261 to 256. You can see here in this figure how it works, total homocysteine and NEM solution, and

it forms this new entity, homocysteine NEM. It has a ratio of 261 and you further fragment it in the second quadruple you end up with very clean spectra, just two fragments, 56 and 215, and we use the 56, which is the major fragment.

Then, we looked at a little bit of the effect of the two different reagents -- reducing agents. So, DTT, we saw that it reacts with NEM, and although DTT does not -- you cannot see positive ion mode, this complex, you can -- it's ionized very well in tandem mass spectrometry and creates a lot of ions suppression for all the other analytes.

And we saw some evidence that there is also some reaction with acylcarnitines. So, at that point, we said okay, we are not going to pursue DTT as a reducing agent from now on and we're just going to use this step instead. Next slide, please.

So, this is the updated sample preparation with the TCEP-NEM protocol, and in the interest of time, I'm not going to into

details on it. I'm just going to say what you can see in blue, these are like the two additional steps that we added. One where we add 12 microliters 30 mM TCEP and shake for five minutes in room temperature to perform the reduction. And then later in the sample prep, we add 40 microliters of 40 mM NEM and shake for another five minutes in order to derivatize homocysteine. Next slide, please.

So, the method actually, it's validated right now, but we have preliminary findings that we can share with you. So, we saw that selective derivatization with NEM increases total homocysteine signal by three to four times. Linearity is great from 2 to about 120 micromole per liter, that's the range that we tested, which includes -- it's great because it includes all the reference range and the disease range for homocystinuria.

Precision, [indiscernible 1:12] total homocysteine with a relative selective derivatization of less than 11.3%. Limits of

quantitation of 2.8 micromole per liter, and no interference detected for total homocysteine. We used the same high-resolution mass spectrometry to confirm that we don't see any interferences.

So, effect on other analytes, which is also important. So, we saw that TCEP and NEM increase the ion-suppression overly but there's still enough sensitivity for all analytes to be detected. And actually, the general standards compensate for this suppression, as you can see in the next slide.

So, C5:1 now was the only analyte that was highly affected but C5:1 uses surrogated internal standard. So, we are currently synthesizing C5:1 to see if we can mitigate that.

So, we did a side-by-side comparison between the two methods. Our current method, which multiplexes amino acylcarnitines with this new method, the TCEP-NEM, the multiplex homocysteine is there, and you can see the results in this graph. So, everything is compared actually to our current method, which

can be seen here by this dotted line. So, if there were no changes, all the other analytes are falling around the dotted line and with the exception of C5:1, you can see that every other analyte is within plus/minus 20% of our two methods. And if you look closely, you will see the ones that are about 20% higher are things that don't have its own internal standard and they use a surrogated internal standard like C3DC and C408, C401, C8. All of those are at about 20%. Everything else is within this 20% range.

And even for those analytes that I just mentioned, they actually pass decision criteria during validation. So, all you have to do is slightly modify your cut off to account for the slight change. The only analyte that didn't pass our decision criteria was C5:1. Next slide, please.

So, of course we wanted to try our method with the newborn screening specimens, so we reached out to Texas Newborn Screening and we asked them for some normal specimens, some

specimens from babies that were administered with total parental nutrition, and then some -- as many as they could afford confirmed specimens.

So, they gave us two of them, which were actually very interesting specimens, because they came from babies that were missed on the first screen but they were actually identified on the second screen based on the timings measurements. As a reminder, Texas is a two-screen state, so they collect the two specimens per baby.

So, as you can see here from the Texas first screen results, methionine concentration for these two babies, it was in the low 50s to low 60s and while the methionine cutoff, the average between the US newborn screening labs, it's about 74.

So, if you're not doing secondary screening, probably your cutoffs are lower than this particular tier screening results and probably the babies could be missed at birth.

So, unfortunately, actually we would

have loved to -- to -- to analyze the first-screening specimens, but they were not available, so we will provide the second-screening specimens and these figures show the results of all these analyses. So, on the X axis, you can see the methionine concentration at micromole Y axis total homocysteine concentration, and these lines represent cutoffs just for visualization. So, we have methionine cutoff, which we use the average of US newborn screening at birth for methionine and total homocysteine cutoff, which is actually the 1 percentile of homocystinuria disease and the source is clear.

So, you can see green, it's on the normal specimens on the left bottom side of the figure. They're all clustered together. They have low total homocysteine and low methionine. You can see that TPN specimens, they have -- they can have very high value for methionine. But low total homocysteine. None of them passes our cutoffs. Only the confirmed homocystinuria specimens have really high, almost total

homocysteine concentrations and they were able to be identified with this method.

So, newborn screening specimens work really well with this method. So, we are pretty happy with that. Next slide, please.

So, to sum everything up, as you already heard, homocysteine, it's a more clinically relevant screening biomarker for homocystinuria than methionine and should be included into homocystinuria screening algorithms.

We feel that if we multiplex LPC-C26 with organic acid and amino acids in one assay, we can generate enough specimens for daily in-house use.

We demonstrated some proof of concept, where you can actually analyze first-tier and second-tier analytes by using separation before analysis by tandem mass spectrometry. And we feel that this would play a significant role in the future, especially as more and more disorders are added into the RUSP and some of

those biomarkers will need to be multiplexed with amino acids.

And finally, we're able to come up with an overlap assay that is multiplexed homocysteine into primary flow-injection analysis tandem mass spectrometry and it could, we hope, streamline the use of homocysteine as a screening marker for homocystinuria in a similar way that succinylacetone multiplexing did for Tyrosinemia type 1. Next slide, please.

Last, but not least, this work wouldn't be possible without my colleagues at CDC, especially Austin who did most of the work that I'm presenting today, the analysis visualization included. Matthew was the person that did most of the development of the second-tier screening method, and Samantha contributed in several projects.

I would also like to thank my boss, Dr. Carla Cuthbert, for allowing us to work on those -- all those exciting projects and giving us the resources to do so and, of course,

Patricia Hunt and Susan Tanksley from the Texas Newborn Screening Laboratory for sharing those residual newborn screening dried blood spots and allowing us to validate our assays. Next slide.

That's it. Thank you, and I will be happy to answer any questions.

CYNTHIA POWELL: Thank you, Drs. Pasquali, Matern, and Petritis, for your excellent presentations. We have time for a few comments or questions. I'll take these first from Committee members, then organizational representatives. Please use the raised hand feature in Zoom when you'd like to make comments or ask a question, and please remember to unmute yourself and state your first and last names. Shawn McCandless.

SHAWN MCCANDLESS: Thank you to all the speakers. That was really interesting and I just want to -- I want to amplify a couple of things and thank the speakers for bringing them to attention and will end with a question. The first is that I -- I just want to point out that

what Dr. Petritis alluded to, at the end, which is that the situation right now with classical homocystinuria in newborn screening is quite similar to where we were with Tyrosinemia type 1 a few years ago where Dr. Matern and others demonstrated that the screening method that states were using was not effective and not sensitive enough to screen for the disorder and it required a change in the approach. And so, I want to thank the speakers for pointing that out.

The second thing is, I would like to point out that the remethylation defects, particularly the ones that are not combined with methyl -- increased methylmalonic acidemia continue to be a very serious health care problem that is -- that is really important for us to address because babies continue to die from these defects, and this is well documented in the literature and the -- this amplifies the problem, because the primary marker would be a low methionine for those defects and without adding the other markers that Dr. Pasquali alluded to

and Dr. Matern alluded to, without adding those additional markers, we're really not going to be successful at screening for those disorders and babies will continue to die either without a diagnosis or with a diagnosis that was made too late. So, I really appreciate the work that all of these people are doing toward that end.

The last thing is I want to specifically thank Dr. Matern for two comments. One is for pointing out that the problem with the lack of a uniform newborn screening system across the country, that really inhibits us from achieving the promise -- the full promise of newborn screening programs.

The second thing I would like to thank you for, Dieter, is the -- the comment about the problem of false positives because right now, the number of false positive screens in all of the tests that we're adding are really limiting our ability to add new tests without -- without the potential harms due to false positives, sinking the boat of newborn screening.

And you've heard me say this before, but I think that it's absolutely critical that people like the three speakers today continue to push to improve our newborn screening methods, as well as state labs and other researchers around the country and world because we have to reduce the number of false positives or else we're going to -- we're going to really run into a roadblock of adding new conditions because of the burden of the -- of the increasing false positives. Right now, in most newborn screening systems there's ten false positives for every true positive. So, for every condition we add, we're adding ten times as many false positives and so that the burden of the false positives eventually sinks the ship, and we must address that.

And finally, I'll stop making comments and ask a question. For Dr. Pasquali, you said that -- you said that adding a second-tier test can both -- it can reduce false positives, but it can also reduce false negatives. Can you just tell us how the addition

of a second-tier test reduces false negatives?

MARZIA PASQUALI: Yes. Thanks for asking that question. And we know that, again, there is noise in the newborn screening and one of the solutions sometimes to decrease the noise is to act on the decision limit and perhaps increase the value of this decision limit, which is going to increase the number of false negatives. Now, if you have available second-tier test, that will allow you to tease out all of those that have not really -- all of those infants who do not have the disease, then they you can reduce your decision limits and in this case, avoid the false negative as well.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Thank you. Jennifer Kwon, Committee member. I'm going to make it clear that I'm not a metabolic geneticist. But I am somebody who thinks about homocystinuria from the child neurologist point of view. So, I think, first of all, I appreciate the comments about trying to reduce false positives and trying

to reduce the number of times we have to interact with families to get new samples, et cetera, as Dr. Matern brought up. This may not be an appropriate question for this group of speakers, and I thank you all for excellent talks, but I was just trying to understand how the CDC Quality Assurance Program, when they -- when they're sort of testing newborn screening labs for their ability to detect these conditions, what -- what role might they play in helping to improve the quality of homocystinuria screening? And again, this may not be the best question for this group of speakers, but I'm curious about your -- your thoughts.

CYNTHIA POWELL: Any of you want to take that on?

KOSTAS PETRITIS: That's a kind of a tricky question. You know, we at CDC, we do have a testing program and we do for our first-tier screening, homocysteine -- first-tier screening for homocystinuria and we do provide the specimens that have just methionine as a marker.

And, you know, the limits that we set, it's, you know, what has been identified for the majority of the laboratories. So, we are actually in the process of introducing a new program for secondary screening analytes. It's going to be a new proficiency testing program that will include a lot of the second-tier screening of analytes, including total homocysteine and, you know, leucine, and all the usual suspects, and I think this will help laboratories towards not only doing methionine, but doing -- testing their platforms for total homocysteine as well.

Other than that, you know, we can just identify gaps that are currently in newborn screening and, you know, try to come up with new methods and then, if there are gaps, and then train newborn screening scientists. We have an annual workshop that takes place in CDC every year where we train -- have some training in different methods that are out there. So, this will be -- these two methods that I mentioned here, the second-tier screening and the first-

tier screening will be things that we would be a teaching laboratories to perform. And, you know, if there is any request, a pre-call, at least, we are able to send people in the lab to help with any method modification, technology transfer, or anything like that, and I think my boss, Carla, will have a much more comprehensive answer than I gave on the subject.

CARLA CUTHBERT: This Carla Cuthbert from CDC. I think Kostas covered -- covered most of it. One of the things as well, in addition to our own method development strategies internally, which does again, you see that it does take some effort being able to have and arrange with our partnership with APHL to arrange for states to come in and do -- for technology transfer, with respect to our training opportunities. Again, that's been suspended because of COVID. A lot of things have been suspended because of COVID because we don't have access to the laboratories as much as we would like on the property.

But we also have funding

opportunities for the States and we put out a certain number of funding opportunities for the states not just to bring on new conditions, but also to help improve existing conditions and that is really a very significant thing as well, so we really wanted to introduce that into our funding opportunities.

So, it's the sort of thing that, you know, we would like to see a dramatic change, you know, in two years to have every state transition to what we may consider to be an improved platform or testing opportunity. But unfortunately, Jennifer, I really appreciate your question, but these things do take some time and there are other opportunities available for people to improve their activities, but we will just keep trudging and moving forward as much as we can. Thank you.

JENNIFER KWON: I appreciate that and just -- just one last comment. I know there are a lot of hands up there. I think that when I think about a child that was diagnosed with

pyridoxine-responsive homocystinuria. I think about what the relationship you had with the Texas Newborn Screening lab and how -- how important it is to save those dried blood spot cards, right, because he wasn't diagnosed within two years of life and without, you know, so with -- without that primary data to have to go back to, you wouldn't really be able to develop your assays. So, I think, for me, as a citizen, this is another reason to advocate for longer storage of dried blood spot cards so that we can be able to optimize our newborn screening. Thank you very much.

CYNTHIA POWELL: Thank you. We'll take one more question or comment from Scott Shone, but first, Dieter, did you want to respond to Jennifer's question?

DIETRICH MATERN: Yeah, thank you. So, I -- the CDC does a great job in helping laboratories to become technically well versed in the technology. They send out blood spots and they ask for results back mostly in terms of

quantitative data and then maybe whether it's a fleck that is high or low or normal, but it's not really proficiency testing in terms of sending a blood spot and asking what is it.

So, for example, one of our frustrations -- and we sometimes get it wrong -- because we're not allowed to use our second-tier test. So, when we see a C3 that's elevated, we want to do the second-tier test to figure out what it is, but that's not part of the program. So, I think what the CDC should do is focus a little bit more on the interpretive skills of these metabolic profiles.

And I appreciate that it's maybe very difficult if you're not a trained biochemical geneticist. But we're not asking to be a biochemical geneticist. We are looking here currently at 50-plus conditions, so I think that's manageable. Also -- and I'm going to say it only once -- there's CLIR out there to help you and you can use it. So, there's room for opportunity, and we should not just limit it on

single numbers but it's a profile. Thank you.

CYNTHIA POWELL: Thanks. Scott Shone.

SCOTT SHONE: Yeah, I just wanted to ask Dieter a quick question, you know, Shawn mentioned this on SUAC and Tyrosinemia type 1, and it was this Committee who put forth sort of a formal, I don't remember what it was called, a recommendation or acknowledgement that succinylacetone was the best marker to screen for Tyrosinemia type 1 and that helped, I believe, it helped a lot of programs get across any barriers that they may have been having internally with either procurement of supplies, equipment, et cetera, et cetera, to get there, you know, some of those late adopters.

Dieter, do you think that this Committee needs to consider that same pathway for homocystinuria and help drive some of that innovation and advancement through CDC's help? I would also say, you know, APHL has their bio -- their newborn screening fellows, and we are a

state that are looking to bring on a fellow to do second-tier testing for homocystinuria. So, that's something that we're doing here. So, I think there's a lot of pathways. But do you think that we should consider that the Committee or, I guess, the next Committee -- it won't happen this time with me sitting here -- but for that for a future?

DIETRICH MATERN: I think so, yes. Apparently, it worked for succinylacetone and succinylacetone, the problem was solved before that discussion started, and I believe it started in 2011 just before I joined the Committee. And what I think happened after the paper was published and endorsed by the by the Committee is that Perkin Elmer either started or finished working on adding succinylacetone to the FDA-approved kit. Now, if Dr. Petritis is successful and finds a way, and I'm sure that Perkin Elmer is watching and listening and talking to him, it may be a natural evolution.

But, I think that the Committee, if

they made a strong statement that you cannot just pretend to screen for homocystinuria, but you actually should do it for the benefit of the babies, that makes a difference.

CYNTHIA POWELL: Thank you. Thank you once again to all our speakers today and I'd also like to thank the HCU Network of America for bringing this to the Committee's attention. We'll continue with HRSA and other stakeholders about this, and maybe using what was done for succinylacetone to have a national dialogue around this marker and anyway, we look forward to moving forward with this and helping to solve this -- this problem.

Next, we will go to our public comment period.

PUBLIC COMMENTS

CYNTHIA POWELL: As I mentioned in my opening remarks that the main meeting will have two public comment periods. Today, we'll hear from seven members of the public who registered to provide these oral comments. We

also received three written versions of the oral testimony that we will hear today.

First, we'll hear from Danae Bartke.

SCOTT SHONE: Ma'am, you're muted.

DANAE BARTKE: There we go. That would probably help if I -- you could hear me. I just want to start by saying we appreciate the opportunity to come before you and make comment again at this event.

My name is Danae Bartke and I'm the Executive Director of HCU Network America. At the age of 10, I was diagnosed with classical homocystinuria, along with my brother was 4 at the time. At diagnosis, while I was asymptomatic, my brother Derek had missed every major milestone by an average of 6 to 18 months and he still continues to feel the repercussions today.

When his lenses dislocated, we finally had the missing piece of the puzzle that gave us our diagnosis. My late diagnosis meant years of struggling with the current treatment of

the low-protein diet, which eventually led to the blood clot. I'm lucky to be here and not be impacted as severely as other patients and be able to lead this patient organization and speak to you today.

There are estimates in literature that at least 50% of patients are missed by the current approach of screening for might methionine. Currently, labs have methionine cutoffs ranging from 45 to 100, and even one lab of 150. These estimates support by analysis of medical claims data as well as the genetic databases looking only at specific defects shown to cause disease and both analysis would suggest there are even more patients being missed. Many who suffer later in life from premature stroke, of blood clots, and other issues.

We have reached out to our patient community in the US and identified 24 patients across 12 states who were diagnosed within the past 32 years but were missed by the newborn screening that was in place at the time of their

birth, 16 of whom were missed within the last 10 years, 22 of those 24 were non-pyridoxine-responsive patients, the more severe type.

We believe that we have only scratched the surface. In our first presentation, we shared with you three patient stories of children who suffered blood clots with one who eventually passed away. This continues to be the story in our community.

A late diagnosis usually means irreversible damage. Late-diagnosed patients experience a variety of symptoms that Dr. Pasquali spoke of. Unfortunately, after patients experience these symptoms, there's no way to undo the damage that has been caused. The only way to prevent these issues is to be diagnosed early and start treatment immediately. An improved screening approach would give more patients a better quality of life with lesser chance of risk associated with the disease.

We know that all of you and the leaders and staff of the state newborn screening

programs and labs wanted to detect all patients at birth to give them the best chance of optimal care to avoid serious clinical sequela.

We all believe the best long-term approach is ensuring diagnosis of all HCU patients is to ensure a first-tier screen of total homocysteine.

We are thrilled to see the progress and commitment the CDC has made, as you heard from Kostas, and we will support other researchers who may have leads on how to do so.

So, while the first-tier screening may be coming in a few years, you heard this morning, there are better solutions to detect for homocystinuria that can be implemented today.

Some states in the US have adopted these lower cutoffs and adopted a second-tier screening that we have seen this has proven in a much better approach. This approach was first used by the Mayo group, which you have heard Dr. Matern speak of. Others have picked up on second-tier screening approach with or without

modifications, and a 2019 publication from EHAD [phonetic] reiterated the importance of this approach.

A few states in the US are already taking advantage of this approach and have started contract -- have contracted with Mayo or other states to provide second-tier testing. This approach also includes a low methionine cutoff that would flag remethylation disorders, which include the majority of the cobalamin disorders and severe MTHFR, all which now have evidence within the past year of publication for early detection and treatment, which provide better outcomes.

Since our first public comments at the ACHDNC meeting in 2018, we have been meeting with state newborn screening labs. We have been working to learn about their current approach, discuss whether a revised approach makes sense, and determine whether we can help in any way to bring forth a revised approach. We are pleased that some labs have already started to make these

changes, including lowering their methionine threshold and implementing a second-tier screen for homocysteine.

We are starting to see positive results. Others would like to initiate the changes but don't have the resources, but are hoping once the pandemic is less problematic, they can figure a path forward.

We know this is a complex area and this solution requires resources. We would urge the Committee to prioritize this effort, which many described during the April 2018 meeting as low-hanging fruit.

We would suggest an endorsement by the ACHDNC of a two-tiered approach that would help make this the priority at a state level, along with the encouragement of the ACHDNC of working along to establish a first-tier screen for homocysteine.

While it could be tempting to wait for the new screen to take action, we suggest not doing so that the number of patients being missed

each year and the uncertainty as to whether and when the first-tier screening will be available.

In closing, the HCU community would like to thank you and the Committee for hosting the Newborn Screening Panel on HCU and would like to ask the Committee to continue pushing the dial for it and urging and assisting state to make these necessary changes. Thank you.

CYNTHIA POWELL: Thank you. Next, we'll hear from Terri Klein.

TERRI KLEIN: Good morning, everyone. My name is Terri Klein. I'm the President and CEO of the national MPS Society and one of the nominators from our organization for the recently approved MPS II RUSP nomination by the Advisory Committee on Heritable Disorders in Newborns and Children, all of you.

I've spent two decades advocating for MPS and ML disorders, as my youngest daughter was diagnosed with mucolipidosis. In 1999, we were not given any hope for her having a long and productive life, but those in her care were

mistaken. Today, she is a patient scientist working in clinical trial designs for rare diseases in Raleigh, North Carolina.

I share this story because rare diseases like MPS II/Hunter Syndrome struggle for awareness and can be devastating for a patient and their families, but science has changed everything.

Over the past two decades, MPS II has seen incredible science and discovery. Researchers, pharmaceutical companies, and patient advocates have been relentless to pave the way to save these boys and men from the devastation of the disease. And with these incredible discoveries, there has only been one obstacle in the way -- screening the babies for MPS II.

The sophistication of newborn screening with the first- and second-tier testing would benefit the patient community for Hunter Syndrome. As we begin to unlock further the implications of the testing modalities, we have

the capacity to change the outlook of a newborn baby with MPS II that include the neuropathic forms of Hunter Syndrome, as we have current therapies abroad and clinical trials ongoing in the United States that are addressing this very issue.

As a leader of a 50-year organization, I speak for our board of directors and our team that we are ready and prepared to support and educate every family that will be screened for Hunters Syndrome in this country, and I don't say that lightly. Our community has worked diligently to ensure we have the social workers on staff and advocates to guide and support these families. Education, equitable access to treatments, and reaching the diverse population of boys with underserved cultures is critical to our mission. We are already working state by state to add and assist state health labs with literature on Hunter Syndrome.

The Society supports 12 disorders and families from each of these families are

grateful for the approval of the ACHDNC in support of the nomination.

We are a family at the Society and most of these children have grown up with one another, regardless of their MPS diagnosis. The joy was felt from coast to coast, as you voted this past February with 11 to 1 to approve MPS II for newborn screening to the Secretary of Health and Human Services.

Newborn screening is a successful program and I'm certain we will reach all the hopes of the program as Dr. McCandless had just shared with us a few moments ago, we can reach the top.

The ACHDNC's Oversight for Newborn Screening has guided this outcome further and now with your referral to the Secretary, we will wait anxiously for their signature to the Recommended Uniform Screening Panel.

As I close my remarks, I want to reiterate how thankful and grateful the National MPS Society is to have worked with all the

professionals who helped us submit the nomination and to each of you on the ACHDNC Committee. I thank Mia Morrison for dedication to the peer reviews and keeping us on track, to Dr. Alex Kemper, who did an exemplary job of oversight and the technical review, to the University of Michigan team of statisticians, who were patient and answering our numerous questions, and finally to all of you who gave your time so graciously to review the detailed reports and findings.

Thank you for the countless teachable moments, and for your time today. I speak for all the parents. We will have immeasurable joy when MPS II is added to RUSP, as Hunter boys of the future will have drastically better outcomes and quality and longevity of their lives.

Knowing this, you have helped create medical change and medical history, and this is not easy to do. So, thank you.

CYNTHIA POWELL: Thank you. We'll next hear from Dylan Simon.

DYLAN SIMON: Thank you, Dr. Powell and to the rest of the members of the Advisory Committee for the opportunity to be here today.

On behalf of the over 30 million Americans living with rare diseases, the EveryLife Foundation for Rare Diseases is pleased to offer the following comments to inform the Committee's ongoing conversations with the review process for RUSP nomination packages.

The EveryLife Foundation is a nonprofit, nonpartisan organization dedicated to empowering the rare disease community to advocates for impactful science and legislation and policy that eventually lead to the development of and access to a life-saving diagnosis treatments and cures.

The Community Congress is a forum for collaboration across stakeholders, representing over 200 individual rare disease patient organizations in addition to over 100 other health care and biotechnology organizations, under which Diagnostics Working

Group is one of the four working groups of the Community Congress, which is dedicated to ensuring that rare disease communities receive the earliest possible access to the life-saving diagnostic opportunities through newborn screening and other diagnostic tools.

We applaud the Committee's recommended addition of MPS II to the RUSP. Once accepted, implementing the addition of MPS II will provide approximately 38 MPS II babies born in the United States the opportunity to access timely life-saving early diagnosis and treatment. However, we wish to know that, during the Committee's review of MPS II nomination, there were discussions of topics we feel were outside the scope of MPS II review.

During the EveryLife Community Congress Newborn Screening Working Group following the Advisory Committee February meeting, members expressed their concerns directly. Comments were centered on worries that some of the discussions about the community

strayed from the task of examining quality of evidence of MPS II nomination and its of public health system and instead focused on the challenges presented by the current health care system. While such discussions are important and we are grateful for the Committee's commitment to addressing these challenges, we asked the committed to ensure that such important discussions do not become barriers to enabling new worthy conditions from being added to the RUSP.

As a rare disease community, we appreciate the Committee is working to prepare for anticipated increase in RUSP nominations. As the Committee navigates the increased demand, we remind the Committee of the importance of formally including the patient community voice in the pre-process and the importance of expanding your capacity.

As the Committee begins the selection and onboarding process of new members, I request that the Committee commit to seeing all

15-member position filled. By fully staffing the Committee, discussions of nominations and review in the newborn screening ecosystem will benefit from the great expertise and personal experience that a fully constituent Committee will provide.

As the Committee prepares to onboard these new members, we asked for increased transparency of the onboarding process. As an organization dedicated to supporting patient advocates, we want to ensure that the patient voices are represented throughout the onboarding process.

We also request that the Committee include two clinical representatives from the Technical Evidence Review Committee in the Final Review Discussion to help answer questions as they come up during the Committee's final deliberation. The inclusion of these experts will allow for key insights into the impact newborn screening would have on the rare disease community and will allow them to respond to any specific inquiries about the conditions that may

arise.

As the Committee considers how to handle the increasing number of RUSP nominations, we strongly encourage the Committee to focus on expanding their capacity review of these conditions, as opposed to focusing on to prioritize nominated conditions. We worry that focusing on prioritization of conditions can limit the RUSP and close it off to other worthy rare diseases.

The Committee has stated that they are capable of supporting only two evidence reviews per year. We understand that while the Committee may have limited ability at the moment to increase that number, we also ask that you provide increased transparency concerning the docket of pending nominations. We recommend that transparency include a brief synopsis of each meeting of all pending nominations with respective dates and where they are in the process, to include the dates and other relevant information regarding submission to HRSA,

assignment to the Nomination Prioritization Working Group, those undergoing the Evidence Review Group review, and those included with the Evidence Review Discussion and vote. Patient organizations prepare for many years building evidence and developing the nomination package. It requires clear timetables of when the RUSP review could potentially take place after submission.

We are thankful over the last few meetings that the Committee has highlighted challenges associated on newborn screening outside the box. Presentations discussing various workforce uses have helped to highlight how many professionals are connected to the newborn screening.

As more treatments for rare diseases are developed, the newborn screening will continue to look at ways to address these current challenges. However, we request that these need to occur outside the RUSP Nomination Review processes and continue to be a separate activity

of the Advisory Committee.

We appreciate the Committee's dedication to meeting our increasing demands on the nation's newborn screening program and we are especially grateful for your unwavering dedication to a rare disease patient communities.

The EveryLife Foundation and membership of our Community Congress Working Group stand ready to support your work and we look forward to engaging with you in the coming months. Thank you so much.

CYNTHIA POWELL: Thank you. Dean Suhr.

DEAN SUHR: Yes, good morning, and thank you for the time and the opportunity to speak.

As always, we want to remind you of our appreciation of and thanks for the important hard and impactful work of this Committee and the Evidence-Based Review Group, and we'd like to offer a special thanks to Chairman -- Chairperson Powell and Dr. Shone for your service.

Four million babies a year are directly impacted, with some 13,000 babies identified each year through newborn screening. Yet, as we all know, there are many other disorders that could be identified at birth or during childhood.

Just like current screen disorders, screening for all new disorders will save and improve the lives of thousands of additional babies. MLD is one of those disorders. MLD newborn screening is a pilot study in the US and abroad. In the US, MLD patients are already being treated with the gene therapy that was approved in the EU by the European Commission in December 2020, about 18 months ago, and it's on the path to a formal US review and approval. We hope to submit an MLD RUSP nomination for your review in the near future. But, that's not the topic of my comments today.

Empowering and increasing the operational capabilities, impacts, sustainability, and continuous improvement of the

Committee are key needs and areas that advocacy is actively interested in and actively supporting.

These external efforts are carried on in many ways, through individual and umbrella organizations at the state and federal levels, including not only in public health, but also in awareness, education, family support, research, therapy development, therapy access, and reimbursement, and legislative policy and development and implementation, as well as appropriations in support of that policy. All of this resulting in improvements in quality of life for newborns and their families.

My comments today focus on the nomination of the EveryLife Foundation for Rare Diseases to be an organizational representative. I previously provided the Committee with a formal written letter of support and will not reread it here, but I did want to highlight some of its content.

The EveryLife Foundation meets the

organizational representative requirements. They have wide-ranging newborn screening and heritable disorders interest in activities. They're already actively informing the Committee -- we just heard from Dylan -- through their Community Congress's Newborn Screening Working Group, they represent dozens, if not hundreds of organizations and disorders, as they form recommendations and develop programs and activities in support a newborn screening.

In newborn screening specifically, with the Newborn Screening Saves Lives Reauthorization, they not only supported the 2011, 2014, and 2019 reauthorization, which, as we know now is still pending a 2022 reauthorization. But they're working to expand the content of the bill to be able to support expansion of Committees, the Committee's impact and capabilities, with budget to improve your operational capacity and state support activities.

They are very active in RUSP

Alignment. This is legislation that ties your Recommended Uniform Screening Panel to activities at the state levels to either review or implement screens that are approved by this Committee. They started in 2017 with RUSP Alignment in California and were quickly followed by Florida, and there are now at least five states with formal RUSP Alignment legislation and 20 states this year during their 2022 sessions that introduced RUSP Alignment bills.

Their Community Congress Newborn Screening Working Group is focused on helping the community to be more informed, educated, organized, and impactful.

More broadly, the EveryLife Foundation works on awareness, novel and efficient research approaches, empowering and educating advocacy to impact clinical trials and regulatory and reimbursement approvals to actively develop innovative and new policies resulting in legislation and appropriations in support of these efforts.

They will bring all of this experience and effort to newborn screening so that you can continue, so that you will benefit from these parallel offers.

In support of all these efforts, they recently completed a National Economic Burden of Rare Disease Study, formally identifying and publishing a trillion dollars of annual direct and indirect rare disease costs. These sorts of efforts help to quantify the impact of timely diagnostics and therapeutic access and other aspects of the Committee's work and recommendation.

In closing, I strongly suggest that the Committee consider the EveryLife Foundation as an ideal organizational representative to not only inform the Committee, but also to magnify the impact of your work.

Thank you for your work, thank you.

CYNTHIA POWELL: Thank you. We'll next hear from Kim Stephens.

KIM STEPHENS: Thank you, Dr.

Powell. And thank you for providing me with this opportunity to offer comments to this Committee today.

My name is Kim Stephens, and I'm President of Project Alive, which is an MPS Research and Advocacy Organization. I'm also the mother of a boy with MPS II.

But today, I'm speaking on behalf of the 30 million Americans living with a rare disease and as co-chair of the EveryLife Foundation's Newborn Screening and Diagnostics Working Group.

As we've heard before, the EveryLife Foundation 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 an access to life-saving diagnoses, treatments, and cures.

Over the past year, the Advisory Committee has reviewed and updated its processes

including efforts focused on ensuring patient advocacy organizations have a better understanding of the RUSP nomination process and the role that patient advocacy organizations play in newborn screening and RUSP nominations.

As the Advisory Committee and HRSA begin to review the nominations for the two open Committee positions, we urge the Advisory Committee to include a patient advocacy organization representative as one of these two members to be appointed, ensuring that this constituency is represented on the Committee, as it has been in the past.

An appropriately qualified patient advocate is an expert on their rare disease and they can provide insight on the impact newborn screening can have on the rare disease community.

Patient representatives can lend their experience, which often includes being a patient, a parent, a caregiver, a scientist, a policy expert to the nomination review process, providing a distinct understanding of the

significance of early diagnosis and treatment.

Patient representatives lend insight into how families juggle the cost of treatment and how patient communities, and providers can support families diagnosed through newborn screening.

It is essential that the Committee once again incorporate this perspective into the work that they do both during the RUSP nomination process and their work outside of the RUSP.

Continued inclusion of a patient advocacy organization representative as a Committee member can also build trust and understanding in the Committee has worked to foster with these organizations. It can signal to the patient advocacy community that our voice remains important. It's not only the RUSP review process, but in discussions about how to improve the newborn screening system and prepare it for the influx of new disorders.

Including the advocate's voice builds diversity inclusion on the Committee and

encourages further discussion and input by these patient advocates.

The inclusion of a patient advocate can help to alleviate fears that problems outside of issues specific to a disease nomination may prevent a disorder from being added to the RUSP or that in the absence of an authentic advocate voice, non-patient advocates speak erroneously on the advocate perspective during Committee deliberations.

Patient advocacy organizations are a vital piece of the newborn screening system and must have meaningful input on Committee decisions that have the power to affect the entire newborn screening ecosystem.

Representatives from patient advocacy organizations come from diverse backgrounds and they can bring their own set of expertise to the Committee.

Patient representatives can serve as a bridge between the patient advocacy community and the Committee, fostering more buy in and

support from even the most skeptical patient advocates.

Like the Committee, advocacy organizations want to ensure that we build a strong newborn screening system that can provide life-saving diagnosis to newborns and that could withstand the many challenging challenges that it faces now and in the future.

As the Committee and HRSA consider adding a patient advocacy organization representative, we encourage you to define what is meant when you consider a patient advocacy organization. The National Health Council set standards for patient organizations interested in becoming members of the Council and we ask the Committee to consider these standards when defining a patient advocacy organization.

These standards require organizations to be engaged in research, professional education, public education, and health promotion, health services, community services, advocacy, or social action. So, when

considering a patient advocacy organization representative, we encourage the Committee to define patient advocacy organization as an organization engaged in one or more of these areas.

We also ask the Committee to follow National Health Council standards and define a patient advocacy organization as an organization that has been active in the space for no less than three years.

We are grateful for the Committee's previous inclusion of a patient advocate as a Committee member and for all the work that is occurring within the newborn screening space and for all the updates the Committee is making to the RUSP nomination process.

We are committed to working with the Committee to incorporate the patient voice more thoroughly by including a patient advocacy organization representative on the Committee.

On behalf of the EveryLife Foundation for Rare Diseases, Community Congress

Newborn Screening and Diagnostics Working Group, thank you for your time and consideration.

CYNTHIA POWELL: Thank you. And finally, we'll hear from Kim Tuminello, followed by Heidi Wallis regarding GAMT deficiency.

KIM TUMINELLO: Good morning. My name is Kim Tuminello and I am the Director of Advocacy for Association for Creatine Deficiencies and co-founder, and I am also a mother of two GAMT children, one that was diagnosed at 10 months and a younger sibling that was diagnosed in utero and treated since birth, and I can tell you as a mom, that they've had two very different lives and they will continue to have very different lives.

I just want to take a quick moment and thank this Advisory Committee for their service to Newborn Screening Program and I want to thank the Evidence Review Board for taking this past nine months to review GAMT in depth. I know it's been a journey for all of us. I'm confident that GAMT has once again proven itself

to be the no brainer of newborn screening. It's easily detectable with its elevated guanidinoacetate and almost non-existent false positive rate which, as this company discussed earlier, is extremely important. It's an incredibly easy treatment that could literally be ordered online and safe and, most importantly, an effective treatment.

It's been six years since we started this journey, almost to the day, of nominating GAMT for the first time, and we were given the word that we needed to find a baby during a newborn screen and I'd like to thank New York and Utah for both taking on that challenge and screening and as luck would have it, Murphy's Law, we found those babies within a certain quick amount of time, close to each other, which I think is really exciting and I think it proves the point that there is a need for the universal screening of GAMT. Those babies have a really bright future, which is incredibly exciting, and as a parent and a community member, I'm really

excited for today. I'm excited for the vote and I'm excited to see the Secretary sign GAMT into newborn screening and, again, I just really want to say thank you to all of you for your work.

HEIDI WALLIS: Thank you, Kim, that was great. So, my name is Heidi Wallis. I'm the Executive Director for the Association for Creatine Deficiencies. You all are probably tired of seeing my face and hearing from me. So, thank you for your time today and over the past six years. Thank you also to the Evidence Review Committee and for your inclusion of myself and my participation in the process on the Technical Expert Panel. It was very well thought out and I have -- I have lots of faith in Dr. Kemper's report and all the work that was done. So, thank you very much for that.

And, you know, looking at what does it take to add a disorder to the RUSP, what are the requirements? I believe that the report and all the work done is going to answer a lot of questions. So, I thought that I would just take

a quick moment and take you on a little live research field trip and introduce you to my two children. This is, you know, throwback to the old days when we used to get together in person for this meeting and I, full disclosure, I have not talked to either of them about the questions that I will be asking, and I just thought that this would be an appropriate way for you to get to know them.

So, can you tell everyone what your name is?

SAMANTHA WALLIS: My name is Samantha Wallis.

HEIDI WALLIS: And how old are you?

SAMANTHA WALLIS: 18 years old.

HEIDI WALLIS: 18, that's right. Okay. And what grade are you in at school?

SAMANTHA WALLIS: I'm nn -- at school.

HEIDI WALLIS: What grade? What grade? Can you tell them what grade you're in?

SAMANTHA WALLIS: 8th grade.

HEIDI WALLIS: You're in 12th grade, silly.

SAMANTHA WALLIS: 18.

HEIDI WALLIS: Okay. Let's ask you another question. Why do you take creatine?

SAMANTHA WALLIS: Because it's important.

HEIDI WALLIS: It's important? That's very good. Thank you. And have you had a seizure?

SAMANTHA WALLIS: No.

HEIDI WALLIS: No? Not today, right?

SAMANTHA WALLIS: Not today.

HEIDI WALLIS: How about, what's your favorite sport?

SAMANTHA WALLIS: Tennis ball is.

HEIDI WALLIS: Do you like to play soccer?

SAMANTHA WALLIS: Yeah, like to play soccer.

HEIDI WALLIS: Okay. You did great.

Can you tell everybody good bye?

SAMANTHA WALLIS: Good bye.

HEIDI WALLIS: Thank you. Louie, it's your turn. Hurry, hurry. Okay, come sit down. Okay. Can you tell everyone what your name is, please?

LOUIE WALLIS: Louie Wallis.

HEIDI WALLIS: Okay. And how old are you?

LOUIE WALLIS: 10 years old.

HEIDI WALLIS: What grade are you in?

LOUIE WALLIS: Fourth grade.

HEIDI WALLIS: Fourth grade? Yeah. Okay. Why do you take creatine?

LOUIE WALLIS: If I don't, I'll die.

HEIDI WALLIS: Well, you might not die, but --

LOUIE WALLIS: Because I need it.

HEIDI WALLIS: Because you need it, that's true. Have you had a seizure?

LOUIE WALLIS: No.

HEIDI WALLIS: Has Sam had a seizure?

LOUIE WALLIS: Yes.

HEIDI WALLIS: Quite a few. What's your favorite sport?

LOUIE WALLIS: Hockey.

HEIDI WALLIS: Hockey, good -- good answer. Okay, you're done. Thank you.

Okay. Thank you. So, background on my children. Sam was diagnosed at five and has been on treatment for 13 years now. She did show some good improvement and developed some speech after diagnosis, but she's plateaued at about first-grade level and Louie was diagnosed shortly after birth. So, I just -- I'm really excited for today and I hope that we have good news to share with our community. I hope that, you know, our vision for the future is that these new families that join our support group will be joining from a newborn screening and we'll have good news for them. I've had eight new families this year so far in 2022 join our group and one

of them was diagnosed through newborn screening and the other seven, we had to, you know, share the news that it's not always a great recovery and there's a spectrum, but we're optimistic for the future. So, thank you so much.

CYNTHIA POWELL: Thank you very much and thank you to all of our public commenters today.

I will now move on to the next section of our meeting regarding newborn screening for guanidinoacetate methyltransferase or GAMT deficiency.

At the 2021 meeting in August, the Committee voted to move GAMT deficiency to a full Evidence-Based review. We received updates on the Evidence-Based review at the November 2021 and February 2022 meetings. Later this afternoon, the Committee is scheduled to vote on whether or not to recommend GAMT deficiency for inclusion on the RUSP. However, first, the Committee will hear three presentations from members of the External Evidence-Based review

Group on the Evidence-Based review for GAMT deficiency.

After the ERG presentations, Dr. Jane DeLuca and Dr. Shawn McCandless will give the Committee Report on GAMT deficiency, followed by discussion and a Committee vote.

Committee members, while you consider the evidence presented today, use the decision matrix as a deliberation tool. For reference, the decision matrix and the decision matrix guidance were included in the briefing book.

First, assess the magnitude of net benefit and then the certainty about the evidence. Next, readiness and feasibility from a state public health program perspective are assessed.

Now, I'd like to introduce the members of the ERG who will present to the Committee today, starting with Dr. Alex Kemper, ERG Lead. Dr. Kemper is Division Chief of Primary Care Pediatrics at Nationwide Children's

Hospital and Professor of Pediatrics at the Ohio State University.

Dr. Kemper completed his pediatric residency training at Duke University, followed by combined fellowship training in health services 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, he has also served as Deputy Editor of *Pediatrics*.

We'll then hear from Lisa Prosser. Dr. Prosser is Maryland Fisher Blanche Research Professor of Pediatrics and Director of the Susan B. Meister Child Health Evaluation and Research Center at the University of Michigan.

Dr. Prosser also holds an adjunct faculty appointment at the Harvard School of Public Health.

Her research focuses on measuring the value of childhood health interventions using

methods of decision sciences and economics. Her current research interests include newborn screening programs, vaccination programs, and methods for valuing family spillover effects of illness.

Finally, we'll hear from Jelili Ojodu, who is the Director for Newborn Screening and the Genetics Program at the Association of Public Health Laboratories. He is also the Project Director for the Newborn Screening Technical Assistance and Evaluation Programs.

Mr. Ojodu is responsible for providing guidance and direction for the Newborn Screening and Genetics and Public Health Program at APHL.

He received his Master's in Public Health from the George Washington University and a Bachelor of Science degree in Biological Sciences from the University of Maryland, College Park.

I will now turn it over to Dr. Kemper.

NEWBORN SCREENING FOR GUANIDINOACETATE DEFICIENCY (GAMT): A SYSTEMATIC REVIEW OF THE EVIDENCE, PART 1

ALEX KEMPER: Thank you very much, Dr. Powell. I'm pleased to be able to present this final summary of the evidence report, which is provided to members of the Advisory Committee in the briefing book.

So, as you all know, I'm going to provide again the summary of the guanidinoacetate methyltransferase deficiency. Next slide, please.

Of course, I'd like to thank members of our -- of our Evidence Review Group who have worked tirelessly to put this together and I'd also like to give special thanks to Dr. DeLuca and Dr. McCandless for serving -- in the role of serving as liaisons to our group. Next slide, please.

And, of course, we have a really wonderful Technical Expert Panel, who worked very closely to make sure that we were asking the

right questions and appropriately evaluating the evidence in a full manner. The Technical Expert Panel also included individuals who submitted the initial nomination form. And so, I'd really just once again like to thank them all for their hard work in helping us put this together. Next slide, please.

So, I'm going to begin first, as I always do, by describing the disease course in epidemiology of the condition here, GAMT deficiency. Next slide, please.

This is an overview of the metabolic pathway leading to creatine development and then creatine uptake in the brain, where it's used as an energy source, which is really a critical function. And what I'd like to highlight -- next slide or next click, there is -- is where the enzyme deficiency is. So, I've circled in here the GAMT enzyme, which is missing or not as functional in GAMT deficiency -- next click, please -- which ultimately leads to the lack of synthesis of creatine and low creatine in the

brain -- next slide, please -- and is associated with elevations in guanidinoacetate.

As I go through this slide, I'm going to remind everyone once again, I abbreviate guanidinoacetate as GUAC, G-U-A-C. It's also sometimes abbreviated GAA in the literature. Just to avoid any confusion, I'm going to just refer to it as guanidinoacetate as I go through the presentation. Next slide, please.

So, in terms of the disease course, first of all, it's important to recognize that the fetus is protected from GAMT deficiency because of active transport of creatine. However, after birth, there is progressive neurological impairment. But it's typically not apparent until at least three months of age and often longer, as you'll see in a little bit.

Untreated GAMT deficiency is associated with significant intellectual disability, limited speech development, recurrent seizures, behavioral problems, weaknesses -- weakness, and movement disorders.

GAMT deficiency in and of itself is not associated with an increased risk of mortality; however, some of the comorbid conditions, for example, epilepsy, certainly can be associated with an increased risk of mortality. Next slide, please.

In terms of the pathophysiology, I showed you before, how low creatine emerges because of the deficiency of the GAMT enzyme, and that's what leads to intellectual disability. The guanidinoacetate accumulation is what's thought to lead to the epilepsy and the movement disorders, that are associated with GAMT deficiency.

In terms of identifying GAMT deficiency and following it over time, the biomarkers associated with creatine and guanidinoacetate, as I've mentioned, and it's also possible to use MR Spectroscopy.

I'm not going to be talking much about MR Spectroscopy, but I do think it's important to recognize that that's a way to

identify, for example, the low creatine in the brain. Next slide, please.

In terms of the genetics, it's an autosomal recessive disorder and there are more than 50 variants that have been described. There are a number of gene frequency studies that have been done. For example, there was one study that was based on multiple gene databases that were combined and based again on gene frequency alone, it was estimated to be about 0.04 cases per 100,000 when you sort of extrapolate based on that. But those combined gene databases can sometimes be biased, especially if they include, for example, mostly older individuals. There was one study looking at gene frequency based in dried blood spots in the Netherlands that estimated a frequency of GAMT deficiency to be 0.4 per 100,000, equivalent to 1 in 250,000. Again, I've mentioned before that the issue of generalized ability of genetic databases is a potential limitation.

The other thing is that not all

pathogenic alleles might have been characterized and that would lead to an underestimate of the frequency. Next slide, please.

But working with the Technical Expert Panel, we suggested a baseline estimate for GAMT deficiency is 0.4 per 100,000, again, equivalent to 1 per 250,000. This estimate comes from that dried blood spot study that I showed you in the Netherlands, as well as a separate study that identified 5 cases in Utah over about a 10-year period that had an estimate of 0.88 per 100,000.

Again, determining prevalence can be -- can be challenging and these can diverge from newborn screening based on how cases are detected. And then, the other thing to remember when evaluating rare conditions is that small numbers can lead to heterogeneity in estimates and then the other thing is that there may be differences in the prevalence based by geographic area. For example, there's a founder effect, that kind of thing. Next slide, please.

In terms of when GAMT deficiency is identified clinically, there's really a wide range. So, for example, there was one study that suggested a median age of about 12 years with a very wide range to 29 years. Identifying the rare conditions and getting to diagnosis is challenging and I highlight here one study, which was a study of nearly 6,400 subjects with unexplained neurologic symptoms and found 7 cases, of whom 6 had signs before 2 years of age. So, this is a research that was specifically interested in GAMT deficiency and went and evaluated in that population.

So, again, when you think about clinical identification, there's this broad range of when individuals come to identification and certainly there's the risk that that some even with symptoms may not come to diagnosis. Next slide, please.

There is a registry, the Association for Creatine Deficiencies, that has put together a registry called Creatine Info, which is hosted

by the National Organization for Rare Disorders or NORD. It was fairly recent when it was developed in March of 2021. It's growing as Ms. Wallis mentioned just a little bit ago and so again, it's still in development and there are no published reports out of it, yet, but I anticipate that much will come from the registry in terms of helping us understand issues related to natural history outcome, and so forth. Next slide, please.

So, now I'd like to dig into issues of screening and diagnosis. Next slide, please.

So, screening for GAMT deficiency is fundamentally based on tandem mass spec for guanidinoacetate and creatine. The diagnosis can be established based on low creatine levels and elevated guanidinoacetate in plasma, you know, a little bit after birth. The molecular analysis, the DNA assessment, can be supportive and the Technical Expert Panel really pointed out how helpful having this information is especially, you know, if there's any uncertainty regarding

the degree of elevation of guanidinoacetate. Next slide, please.

So, I'm going to dive next into programs that have been doing screening or actively involved in screening. The first that I'd like to discuss is Utah. Utah's a two-screen state, each infant is screened twice. Screening for guanidinoacetate and GAMT deficiency began in June of 2015. They use a laboratory-developed test. Between 2015 and 2019, screening in Utah was through ARUP, the Associated Regional and University Pathologists in Utah and it involved a two-tier process. First-tier tests for guanidinoacetate and creatine using tandem mass spec in a derivatized assay followed by liquid chromatography tandem mass spec for guanidinoacetate and creatine.

In 2019, the newborn screening program was brought into the Public Health Laboratory. They still use laboratory-developed tests for their screening, and they are doing everything now through just a one-tier screen

with guanidinoacetate and creatine by flow-injected tandem mass spec and their test is now non-derivatized. Next slide, please.

So, what we've done here is broken out the two periods, 2015 through 2019, where the derivatived method was used, and you can see that there is close to 200,000 newborns screened with 365 positive first-tier screens and 2, which were ultimately sent for diagnostic evaluation after the second-tier screen, which is about 1 referral per 100,000. There were no cases diagnosed during this time between 2019 and 2021. There were about 126,000 newborns who were screened, with 2 positive first-tier screens ultimately leading to 1 case that was identified and during that period, that's equivalent to 0.79 cases per 100,000. But what I did was I combined the full period because I think it gives better insight into the numbers, so that if you combine these two periods and recognize that the methods were different, the referral rate was about 0.9 per 100,000 newborn screenings or 1 per 107,102.

I've listed the numbers both ways, because I know people like one or the other.

And then in GAMT deficiency, there was overall 0.31 cases per 100,000 newborns screened or about 1 case per 321,000 newborns screened. Next slide, please.

So, now I'd like to talk about the New York Screening Program. They've been screening for GAMT deficiency since October 2018. Like Utah, they use a laboratory-developed test. They initially also had a two-tiered screening test with guanidinoacetate and creatine by flow-injected tandem mass spec, followed by guanidinoacetate by liquid chromatography tandem mass spec. Their second-tier screening test was discontinued in 2021 and New York does, as a helpful benefit during the process, so specialty referral, sequence the gene. They provide the molecular diagnosis as part of the referral process. Next slide, please.

So, in 2021, so this is just a snapshot of 2021, they screened a little over

211,000 newborns. There are 82 positive first-tier screenings, of which 5 were referred immediately for diagnostic evaluation. There were 77 of those 82 where there was a request for a repeat test. Importantly, 76 of them were in the neonatal intensive care unit. Of those, 1 was referred, 4 died for reasons that were not thought to be related to GAMT deficiency, and there were 2 pending, but had an initial negative screen, so, unlikely to have GAMT deficiency.

So, if you look across the 6 referrals, there was 1 infant who was ultimately diagnosed with GAMT deficiency. There was 1 infant who was diagnosed with arginase deficiency, 2 were normal, and 2 died for reasons that were not thought to be related to GAMT deficiency before diagnostic evaluation could be completed.

So, if you look across all of 2021, the referral rate for diagnostic evaluation was 2.8 per 100,000 newborn screenings or about 1 per 35,000 or so, and then GAMT deficiency was

identified in 0.47 per 100,000 newborn screenings or about 1 per 212,000. Next slide, please.

Now, what I'd like to do is summarize the entire experience. So, if you look at October 2018 through April 2022, there were 759,246 newborns who were screened. Ultimately, this led to 24 referrals for diagnostic evaluation, which is the equivalent to 3.2 per 100,000 newborns screened or about 1 31,635. Out of that full complemented newborn screen, there was one case of GAMT deficiency that was diagnosed, which is the equivalent of 0.13 cases per 100,000 newborns screed or about 1 case for 759,246. Next slide, please.

Now, I do want to highlight that there's other GAMT deficiency newborn screening activities that are going on. So, in Michigan, GAMT deficiency newborn screening was approved towards the end of 2018. They are going through the validation process and full population screening has not yet started. When Mr. Jelili talks about Public Health System Impact

Assessment, he's going to dig through this issue in particular. Next slide, please.

Screening also is ongoing outside of the United States. So, British Columbia began screening in September 2012. They use a three-tier assay. So, the first tier is guanidinoacetate with tandem mass spec. Then, a second-tier test using guanidinoacetate with liquid chromatography tandem mass spec, and then a third tier, which is targeted gene sequencing. So, referral for diagnostic evaluation is based on all three of those things.

From September 2012 to April 2022, there were a little over 428,000 specimens that were evaluated, 0.3% had a positive first-tier assay. There were 28 with a positive second-tier assay, and then 3 with a positive third-tier assay and who were referred, which is the equivalent of 0.7 per 100,000 newborns or about 1 per 142,713.

They have not yet identified newborns with GAMT deficiency. Next slide,

please.

In Ontario, GAMT deficiency newborn screening was recently approved. They are going through the validation and of the planning processes and they plan to start with the screening in the summer of 2022. Next slide.

Australia, in the state of Victoria, has been screening for perhaps the longest period of time. They began screening in April of 2002. They use a derivatized method with tandem mass spec. So, there have been overall about 1.4 million newborns who were screened, and they've identified 1 likely case.

Now, I spoke to Dr. Pitt, who oversees the newborn screening program in Australia, and it really does seem that this individual, this newborn, does have GAMT deficiency, but he just wanted to be very cautious and so the full molecular analysis was completed. This case was recently identified and so he just wants to caution that there's a small chance that it isn't. But for all intent and

purposes, it really does seem to be an affected individual.

So, if you look at it in an annual basis, they screen about 80,000 newborns for GAMT deficiency each year. There's about 20 that have a second-tier test, which is really re-looking at the guanidinoacetate level that they see on the tandem mass spec. There have been 3 that have had a repeat sample that's been requested and on an annual basis, there are only about 0.3 infants that have been -- that are referred. So basically, you know, like 1 baby every few years gets referred for diagnostic evaluation. Next slide, please.

So, what I've done on this slide is summarize the data that we have by newborn screening program, broken up by time period, the number of newborns that were screened, the number of newborns that were identified as having GAMT deficiency, the diagnostic referral rate, and the case detection rate, and because of the way that the data were available, you can see, for

example, in Utah, we have the screening when it was still being done by ARUP and screening when it moved in-house and was a derivatized approach, and then you can see the purple rows represent the summary data.

So, we have, you know, two rows for Utah, two rows for New York, and then I have the summary value in purple for New York, the summary values in purple for British Columbia, and then the summary values for Victoria also in purple. I'd ask you to take a look at those rows and it really just repeats what I said.

I think that the key point that I'd like to make on this slide is that the bottom two green lines which are pooled data. First, what we did was we pulled the screening data from the US, which covers a period of 2015 to 2022, over which time there were 1.08 million newborns that were screened, leading to the diagnosis of 2 infants with GAMT deficiency. This is a diagnostic -- this was accompanied by a diagnostic referral rate of about 2.6 infants per

100,000 and a case detection rate of 0.19 per 100,000.

The last row is the pooled data for the US and outside of the US. I did that because I didn't want the findings from Victoria to swamp the data that we have from the United States. But if you add in Victoria, there been nearly 3 million newborns that have been screened with 3 cases of GAMT deficiency, a diagnostic referral rate of a little over 1 per 100,000, and a case detection rate of 0.1 per 100,000.

So, I hope this slide sort of gives you a sense of the magnitude of referrals and the range of case detection through newborn screening.

When Dr. Prosser goes over the modeling, you can see how that plays out in a different way, which hopefully will be helpful as you make your decision. Next slide, please.

So, in terms of -- I want to take a step back and summarize the screening data. So, first of all, high-throughput tandem mass spec

screening has been incorporated into two state newborn screening programs, both of which were done as a laboratory-developed test.

The diagnostic referral rate is low compared to other conditions and, as I mentioned before, that there are 3 cases that have been identified through newborn screening, Utah and New York, and I explained earlier where I put likely the case for Victoria. Next slide, please.

Now, I want to transition and talk about treatment. Next slide.

So, first of all, I'd like to remind you of the metabolic pathway that leads to GAMT deficiency, because it gives you insight into the treatment, which is replacing creatine through oral supplementation and ornithine supplements to help with the block, you know, decrease the production of guanidinoacetate sodium benzoate, which can help lower glycine, again with the idea that you want to decrease the buildup of guanidinoacetate. Next slide, please.

So, there is expert treatment consensus around the use of creatine and ornithine supplements as well as sodium benzoate. Again, these are all oral supplements. There is consensus around the degree of supplements that individuals need. There's also consensus around the protein restriction. It's less restrictive and actually, if you go back a slide, I'm sorry, I should have mentioned. There we go. The reason for the protein restriction is to try to decrease the amount of arginine that's going in, again trying to decrease the guanidinoacetate production. Next slide, please.

So, getting back to the protein restriction, there is consensus around the degree of protein restriction and one of the things I'd like to highlight is it's less restrictive for the other metabolic conditions we're used to thinking about like phenylketonuria, for example. So, individuals can still, you know, babies can still breastfeed, that kind of thing, and then there's serum monitoring, which is more frequent

earlier in life.

The Association of Creatine Deficiencies does help families access creatine and ornithine from reliable sources that are manufactured with good clinical practice and sodium benzoate is available from compounding pharmacies. Next slide, please.

There is a gene therapy that is in development. It's delivered with an AAV vector. Thus far, it's been tested in a mouse model and shown to normalize guanidinoacetate concentration. So, you know, gene therapy is always very exciting but it has yet to move into human studies. Next slide, please.

What I'd like to do next is focus on what we know about the benefits of early intervention. So, initiation of pre-symptomatic or early symptomatic stages versus later and given the rarity of the condition, it's not surprising that there's a limited amount of information about that. We did find 6 reports that I would like to highlight on the next slide,

please.

So, this table shows you the individual reports. The last one that's listed, I want to highlight, is just from a meeting abstract that was published. It's not a full report. If you look on the left panel, we described outcomes with treatment onset in early infancy, and on the right panel, it compares those individuals to their older siblings with later diagnosis when that information was available. You can see that there was one study from 2013 where there was no sibling comparison.

I want to highlight a few things. So, first of all, if you look at the first column under outcomes from early intervention, you can see that there's a range from the prenatal period to about 5 months. There was 1 study that included 3 individuals, 1 who was diagnosed during the prenatal period, another at 1 week, another at 3 weeks. The next column shows you the duration of follow-up and the longest period of follow-up here is 42 months, and then the next

column shows the developmental status at this follow-up.

Now, one of the challenges is that these reports, did not have standardized evaluations of development at specific ages and, in fact, the reports generally just have sort of a qualitative assessment of developmental outcome. So, you can see, you know, all those normal. But I can't really give you any more information beyond that.

There is that statement for this study by Dhar, et al. 2009, where they described central hypotonia and developmental delay persists, but that's really as far as I can tell you.

But I want to contrast that first panel with the second panel showing how these children were doing, and again there's variable period of follow-up up to 6-1/2 years in the El-Gharbawy, et al. study from 2013. And what I'd like to highlight is the differences that are described in the outcomes, ranging from speech

and fine motor delays to developmental delay, epilepsy, speaking a few words, and other more significant impact.

Again, these studies generally provide a qualitative assessment of these developmental outcomes and so we're limited in the ability to tell the story, but I just want to sit here for, you know, 10 more seconds so that you can look at this panel again, look at this slide. This is in the report as well, just so that you can compare and see the differences in developmental outcome at follow-up versus their siblings. All right, now, next slide.

All right. So, what I'd like to do is just summarize what we know about early treatment. So, these case series suggest that pre-symptomatic or early initiation of treatments is associated with improved neurologic outcomes, with the, you know, the issue that they don't provide outcomes based on standardized quantitative measures at, you know, sort of synchronized times to make the comparisons

easier. Next slide, please.

I'm going to switch gears now and talk about newborn screening program costs of GAMT deficiency newborn screening, and this is work that was primarily led by Dr. Scott Gross. Next slide, please.

So, the cost data come from interviews with representatives from the New York and the Utah Newborn Screening Programs. Included in our estimated costs were things like equipment, reagents, added laboratory technicians and scientist's time. It's always difficult to look specifically at one screening test when it's incorporated into existing activities, and so breaking out specific costs is challenging. Next slide, please.

That being said, the estimated additional cost to newborn screening programs to screen for GAMT deficiency above the operating costs of the program may be substantially less than $1 per infant. And, if you remember in our method approach to evaluating cost of screening,

we provide ranges and so, the range here is substantially less than $1 per infant. Again, this is based on interviews with the two programs that have implemented GAMT deficiency, and I also want to highlight that both of these programs use the laboratory-developed test, and they have the technical capacity, the ability to validate the test and so forth. So, again, these costs don't necessarily apply to other programs and you're going to hear more about those issues as Mr. Jelili presents the Public Health System Impact Assessment. Next slide, please.

So, we can now move into modeling and Dr. Powell, do you want us to continue, or would you prefer to break for lunch?

CYNTHIA POWELL: Yeah. I think we'll go ahead and take a break now. We're scheduled to reconvene at 1:20 p.m. Eastern time. So, thank you, Dr. Kemper, and then when we start part 2 of the Evidence Review, we'll hear from Dr. Prosser followed by Mr. Ojodu.

ALEX KEMPER: Thank you.

CYNTHIA POWELL: Thanks.

BREAK

CYNTHIA POWELL: Welcome back, everyone. Before we continue with the rest of the Evidence Review Group presentations, I need to take roll. For the Committee members, I think I'm supposed to mention again that Kamila Mistry from the Agency for Healthcare Research and Quality is unable to join us today. Kyle Brothers.

KYLE BROTHERS: Here.

CYNTHIA POWELL: From the CDC, Carla Cuthbert.

CARLA CUTHBERT: I'm here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: From the FDA, Kellie Kelm.

KELLIE KELM: Here.

CYNTHIA POWELL: From HRSA, Michael Warren.

MICHAEL WARREN: Here.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Here.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Here.

CYNTHIA POWELL: From NIH, Melissa Parisi.

MELISSA PARISI: Here.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Here.

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

SCOTT SHONE: Here.

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

ROBERT OSTRANDER: Here.

CYNTHIA POWELL: From the AAP, Debra Freedenberg.

DEBRA FREEDENBERG: I'm here.

CYNTHIA POWELL: From ACMG, Max Muenke. From ACOG, Stephen Ralston. From APHL,

Susan Tanksley.

SUSAN TANKSLEY: I'm here.

CYNTHIA POWELL: From the Association of Women's Health, Obstetric & Neonatal Nurses, Katie Swinyer.

KATIE SWINYER: I'm here.

CYNTHIA POWELL: Child Neurology Society, Margie Ream. Department of Defense, Jacob Hogue.

JACOB HOGUE: I'm here.

CYNTHIA POWELL: From the Genetic Alliance, Marianna Raia.

MARIANNA RAIA: I'm here.

CYNTHIA POWELL: From March of Dimes, Siobhan Dolan.

SIOBHAN DOLAN: Here.

CYNTHIA POWELL: From the NSCG, Cate Walsh Vockley.

CATE WALSH VOCKLEY: Here.

CYNTHIA POWELL: And from SIMD, Gerard Berry.

GERARD BERRY: Here.

CYNTHIA POWELL: Okay, thank you. Next, we will hear from Dr. Lisa Prosser.

NEWBORN SCREENING FOR GUANIDINOACETATE DEFICIENCY (GAMT): A SYSTEMATIC REVIEW OF THE EVIDENCE, PART 2

LISA PROSSER: Great. Thank you very much, Dr. Powell. I'm not seeing the slides yet on the screen.

CYNTHIA POWELL: Dr. Prosser's were in with the ones we -- yeah, there you go.

LISA PROSSER: Perfect, great. Thank you very much.

So, on the next few slides, I'll be reviewing the results for projected population level outcomes using decision modeling. Next slide, please.

And the goal with this analysis is to compare projected outcomes from GAMT deficiency newborn screening for all newborns in the US with usual detection, in the absence of screening. Next slide, please.

So, the approach is to model an

annual US newborn cohort of 3.6 million and to estimate the outcomes for newborn screening, screening outcomes, as well as cases of diagnosed GAMT deficiency, and for clinical identification to estimate the confirmed number of cases for GAMT deficiency. Next slide, please.

The previous models conducted for evidence review have evaluated additional longer-term outcomes, such as death, cognitive impairment, or the need for mechanical ventilation, and this is the second condition for which both shorter- or longer-term health outcomes are not the model due to insufficient evidence to model those outcomes. Next slide, please.

As a brief bit of background using decision analysis here, this is a systematic approach to decision making under conditions of uncertainty and our goal here is to project ranges given the, especially for this condition, the scarce data that's typically available for a newborn screen conditions or candidate conditions

that will present some point estimates for any of the outcomes that really our goal is to provide ranges to the Committee for both screening, as well as when we have it available for short-term outcomes for the Committee to be able to compare those sets of outcomes across newborn screening and states.

Decision analysis allows decision makers to identify which alternative is expected to yield the most health benefit, given the best evidence that we have to date and at the same time can often identify key parameters and assumptions where additional data are needed and so here clearly for health outcomes in past conditions, this has helped to identify where data collection could provide additional information for future modeling. Next slide, please.

This slide shows a simplified diagram of the model schematic. So, the way that the model analysis works is that hypothetical cohorts of newborns are models in each arm of the

models. So, there are two arms, one for newborn screening, and one for clinical identification. You follow the decision tree across the top part of the slide under newborn screening. There's a chance that a newborn will have a positive screen and be referred for additional testing, or that they have a negative screen. If they are referred for additional testing, then there are the following probabilities of a confirmed of GAMT deficiency diagnosis. The possibility of false positive, positive lost to follow-up. In this case, there's also an additional potential outcome here designated as other, which includes diagnosis of non-targeted conditions or unknown determination here -- and I'll go through the numbers on the next slide -- for 2 newborns who died before confirmatory testing could be conducted. Next slide, please.

This slide shows the model inputs used for estimating the transition probabilities and the model. These are all derived using the data that were summarized by Dr. Kemper earlier

in the presentation and summarize the combined data for the Utah and New York newborn screening programs.

Just to run through these quickly, for each of the probability inputs, there is the most likely input that represents again, the most likely estimate for that particular model input, as well as a range. And again, here we're more focused on the ranges than on the most likely value.

So, there is a 1.7 to 3.8 per 100,000 chance of a positive screen. The population level, again this is combined Utah and New York data, for a GAMT deficiency diagnosis, the positive screen 0.2 to 0.6 per 100,000. There's a chance that a positive screen is false ranging from 1.6 to 2.4 per 100,000. There were no newborns that were lost to follow-up on in the data that was provided by the Utah and New York newborn screening programs, but here, there is a slight probability based on if the estimated confidence interval around that zero probability.

And again, here, there was 1 newborn who was diagnosed with a non-targeted condition and 2 that were designated as unknown determination to death before confirmatory testing but are expected to not have had GAMT deficiency. But, again, there was no confirmatory testing there.

Under clinical identification and given the very rare nature of this condition and the model being utilized for the estimate of the range, it is based on the evidence of the estimates that were summarized earlier, which represents a range of 0.05 to 0.5 per 100,000 or 1 in 200,000 to 1 in 2 million for diagnosed cases of GAMT deficiency in the absence of newborn screening. Next slide, please.

So, the results of the decision modeling for a cohort of 3.6 million newborns projects on an annual basis 93 positive screens with the range of 62 to 135, an estimated 7 cases of GAMT deficiency with a range of 1 to 22 compared to clinical identification of a range of

2 to 18 cases per year and 77 false positive cases with the range of 59 to 88, 0 cases lost to follow-up, with a potential upper range there of a range of 0 to 12, and this other designated category of roughly 10 with a range of 2 to 26. Next slide, please.

So, in terms of summary, the modeling projections estimate 7 cases of GAMT deficiency diagnosed with the range of 1 to 22 would be identified annually through national newborn screening. There's insufficient evidence to compare directly to estimated cases detected in the absence of newborn screening, but the projected range there is again 2 to 18.

For this condition, there was insufficient evidence to model any clinical outcomes beyond case identification to quantify the potential benefits of screening.

But to clarify that last statement, just to be clear that this does not imply that there is not evidence of benefit, but insufficient evidence to quantitatively estimate

the impact at the population level.

So, I will stop here and turn it over to Jelili Ojodu for the Public Health System Impact Assessment. Thank you.

JELILI OJODU: Thank you, Dr. Prosser. Can you hear me?

CYNTHIA POWELL: Yes.

JELILI OJODU: All right, awesome. And thank you to Dr. Powell as well for your many years of leadership. I certainly have appreciated your quiet leadership over the years in getting things done. So, thank you, and thank you to Dr. Shone as well for always thinking about the newborn screening system as a whole in your thoughts and input. Next slide, please. Next slide.

So, we have the primary objective of understanding what the Public Health System Impact is for adding new conditions and we work as part of a group of folks, some of them you heard from already, some of them are behind the scene, and this information is primarily

collected from State Public Health programs in order to better understand the readiness and feasibility of adding a condition, in this case guanidinoacetate methyltransferase deficiency or GAMT.

We try to focus on all of the information that is going to be able to help us better understand not only what it will take to be able to screen for GAMT in newborn screening programs, but also other related activities and I'm going to highlight this as I progress in my presentation here. The authority to screen, I should remind everyone, is very important and crucial and without the authority to screen in state newborn screening programs for any of the conditions, none of this will be possible. Next slide, please.

So, how do we define readiness? As I've done over the years in highlighting this in at least two newborn screening programs, the readiness of adding a new condition focuses on the time it takes for them to be able to mandate

population screening within a year, at least that's what we define as those programs being ready, developmental readiness one to three years that a program could implement population-mandated screening, and then longer than three years, is what we would identify or highlight as unprepared for newborn screening programs. Next slide, please.

So, it's also important to highlight the competence of feasibility as defined as part of our survey questionnaire that we send out to state newborn screening programs. Dr. Kemper and Dr. Prosser highlighted a number of these and I'm not going to talk too much about them. You do need a test -- an established test that we can use for population screening, that's definitely important, as well as an approach for diagnostic confirmation, a treatment plan, and established approach for long-term follow-up. Next slide.

So, methods. Next.

As for GAMT, like we've done for other conditions, we developed a fact sheet of

information collected from state newborn screening programs, the ones that at least have been screening for GAMT, to better understand and highlight and share challenges and opportunities to other state newborn screening programs.

Remember, this is a hypothetical for them. The majority of the country does not screen for this particular condition. So, every information that we can gather to help them understand what it will take is very important.

As part of then the fact sheet, we highlight all the things that other states, in this case New York and Utah, are currently doing in form of a webinar to state newborn screening programs. Those state newborn screening programs are the target audience for this particular webinar, and then developed a survey, to be able to get feedback from all of the 53 newborn screening programs, and that includes the District of Columbia.

We did perform in-depth interviews for three newborn screening programs. As you

know, the two that have mandated screening for GAMT, as well as one that is exploring or has been exploring screening for GAMT, and then we conducted two additional interviews. These are phone interviews that we get on the phone and just talk about on everything related to what these states -- what it would take to be able to screen -- publish and screen for GAMT with two other states that are not screening for GAMT at the moment. Next slide, please.

So, the results. Next slide, please.

So, I think Alex had spent a good amount of time talking about this and I'm going to highlight much other than the last two states there, the New York and Utah currently have universal mandated screening for GAMT. The state of Michigan has a mandate to screen and has been trying to validate an assay for population screening for a few years now. I'll highlight some of their challenges later.

And then, we just informed as part

of the survey that the state of Connecticut is or has started to not only consider or look into the implementation of screening for GAMT, but also have started working on the markers and an assay to be able to screen for GAMT in moving forward. They don't have a mandate and there's no current timeline on when universal screening will start there yet. Next slide, please.

So, we sent the survey out to 53 newborn screening programs, 31 or 34 -- 35 responded, I think, of which we excluded 4. The 2 that are either screening for GAMT at the moment, the 1 that has been trying to validate for GAMT for a while and then the 1 that I just -- Connecticut as well, was excluded from the survey.

So, the results of the survey that I'm going to highlight in a minute is going to be focused on the 31 states that do not screen for GAMT at the moment. Next slide, please.

So, over the next few slides, I'm going to highlight the results in this format

here. Excuse me. The question that was asked of these states is please indicate what are the following implementation factors for GAMT deficiency, and what would present to you those states in the form of a major, minor -- or minor challenge? And as you can see here, most of the respondents, approximately 90 percent of them, considered the availability of a validated screening test, addressing administrative challenges, as well as increasing their fee as challenges to be able to screen for, do population-mandated screening for GAMT, once they have the authority to screen for GAMT, of course.

The availability of or identifying specialists and availability of treatment was not deemed as a challenge in these states and so, that's something worth noting in moving forward. Next slide, please.

The question and these questions -- the full questionnaire is included as part of your packet. So, if you want to review all of the questions, they will be there. The question

we asked here is consider of what are the resources needed for your newborn screening program to implement GAMT deficiency? Now, these are states that actually have a laboratory newborn screening program. We asked a different question for states that outsource their newborn screening laboratory testing to other states or a commercial entity.

And as you can see here, approximately half of the respondents from those states, said that not having a method for screening GAMT was going to be a major deficiency. Oh, yes. They were not going to be able to bring on screening for GAMT within a year. So, this was like based on timelines. LIMS capacity, LIMS being Laboratory Information Management System, capacity, and instrumentation interface for reporting out was also deemed as something that states were not going to be able to do or implement within a year.

Let me just read this. Lack of FDA-approved kit also is something that states

mentioned that certainly would be helpful in moving forward, but being that there is none available right now, the two states that are screening for GAMT are using a laboratory-developed test. It is certainly noteworthy.

And then 32 percent of the states reported not having a LIMS capacity to be able to get screening moving forward within a year. Next slide, please.

So, these are the states that outsource their newborn screening to other states or a commercial entity, the commercial entity in this case being Perkin-Elmer. The question is, what resources are needed for your newborn screening program in order to implement GAMT screening?

And again, a good, I think, about 32 percent of the respondents did not have the technical expertise, at least that they thought would be needed within a year to be able to screen for GAMT.

Let's flip side it. A good

majority, three-quarters of the respondents, noted that they, in fact, had the specialists or have contact with specialists or treatment centers and diagnostic services in place for GAMT deficiency.

You can see here that the same goes for, I talked about treatment specialists and appropriate access to diagnostic services. Next slide, please.

So, the full question here is, the following -- these are the considerations to be able to add GAMT as part of your newborn screening programs. I think this is a continuation of the last slide as well. So, these states outsource the laboratory testing to another state or commercial entity.

Availability of a screening test, follow-up protocols all seem to be things that folks say that they thought they do not have, but they could get within a year: appropriate diagnostic testing, as well as the treatment centers similar to the last slide, is something

that they didn't think was the major concern.

And sufficient amount of laboratory staff to be able to do the follow-up and tracking again was something that -- one of the variables that they did say that they had available to them right now and will be able to move forward with GAMT screening in their state newborn screening program. Next slide, please.

The question here is, can you conduct or would you hypothetically be that again, the majority of states are not screening for GAMT. Would you conduct the second-tier test for GAMT deficiency? I think about half of them said that it wasn't necessary, 30 percent said most likely, but they won't be ready to be able to do it within the next year.

That question, we have to be careful about, because I'm not sure if states are considering doing that second-tier in house or not.

And then, 20 percent of them said that they plan to outsource or contract out the

second-tier testing if, in fact, they were to be -- they were doing it and then people said that they could be ready within a year to be able to do second tier in-house. Next slide, please.

The question asked here is please indicate the degree to which the factors impede or facilitate the ability to adopt screening for GAMT in your states.

Again, barriers were cited around majority of the programs, including: the estimated cost per specimen to conduct a screening, the factors related to other priorities that are going on in the state newborn screening program at that point, and other newborn screening program activities. For that, I think they were highlighting the addition of previous conditions that have been added to the RUSP that they haven't added into their state newborn screening panels. Next slide, please.

And then, is this the next slide? Okay, and then this, oh, this is a continuation of the previous slide there because we didn't

want to just have these slides be too busy. Same question and factors that impede or facilitate the ability to adopt screening for GAMT and, as you can see here, the majority of the states were highlighting that the expected cost benefit to screening was definitely a facilitator. The input from advocacy groups, as well as expected clinical outcomes, and the fact that GAMT can be multiplexed with other conditions that dates are currently screening for was certainly a major facilitator in state newborn screening programs that responded to the survey. Next slide, please.

So, estimated time to implement GAMT deficiency in states. Remember these are hypothetical questions that we were asking states. Once they have the authority to screen for GAMT, once they had the funding, once they have been able to procure ideally all instrumentation, educational activities, all of that, in their states, about half of the states respond that it will take about 24 to 36 months

to be able to -- 25 to 36 months to be able to implement GAMT in their state newborn screening programs. Next slide, please.

So, I highlighted the fact that we did some extensive interviews with the states that are currently screening for GAMT and most of these have already been highlighted by Alex. The fact that GAMT can be multiplexed with other amino acid and acylcarnitine is a plus and certainly a plug and we're almost always thankful for the fact that we -- this is a laboratory-developed test and if not for that, we won't be screening for this condition at this point in time.

The states that are screening highlighted the fact that the additional staff time -- there is little additional staff time required. And, as Alex noted, second-tier test was eliminated by both of the states as they progress in screening for GAMT in their newborn screening programs.

I talked about the laboratory-

developed tests and then the challenges again include not having an FDA-approved kit and in some cases, making adjustments into the LIMS system. Next slide, please.

So, Alex talked a little bit about this. We spoke to the folks in Michigan, and they talked about some of the challenges in validating their method for screening for GAMT. This is they were trying to use or explore using the non-derivatized kit that they use to screen for other mass spec conditions. Change that to screening for GAMT, which will then change the kit into a laboratory-developed test, and they've spent the last on and off three years in trying to validate that kit or that kit to LDT to screen for GAMT without any success.

There were some sensitivity issues. They noted for a while there that there were high false positives that were flagging, not only for GAMT, but for all of the conditions on a plate that they had to resolve by extensive cleaning out their mass spec being that it's a non-

derivatized method that they were using. And I think in moving forward, which they plan to figure out a way to move forward in screening for GAMT, one of the things that they mentioned was replacing their mass specs, which were a little bit older, and maybe considering changing their methodology to a laboratory-developed test. So, more information on that later from the program. Next slide, please.

So, lesson learned from states that are not screening for GAMT, we heard from two states and, as you can imagine, they highlighted a few things, including competing priorities. Competing priorities in a newborn screening program can be anything from continuous quality improvement project, it can be adding other conditions that is on the RUSP but the state doesn't screen for, the funding to be able to get, to be able to support not only newborn screening in the laboratory, but all aspects of the system, updating their LIMS system, the Laboratory Information Management System.

And then, the concern about expectation in newborn screening programs not having enough resources to be able to do all these things in a timely manner, whether or not there is an alignment to the RUSP in a limited amount of time if the state doesn't have the authority to screen and if procurement of the laboratory equipment takes two years, it then becomes a major issue for the states to be able to move a number of things for it and they noted that as part of their challenges in moving forward. Next slide, please.

The strengths, we got about 66 percent of folks responding to the survey. The webinar and fact sheet was absolutely helpful in helping states understand what to expect in moving forward if they were to screen for GAMT. We pretty much tried to show them through other states what to expect and implementation of GAMT in their newborn screening programs, and it certainly helped to show and highlight those real world experiences and working the path of the

spot. Next slide, please.

The limitation, of course, is that again, and I've said this a number of times, these are subjective responses for a condition that a state has not been -- is not screening for and we know that going in asking these questions in the first place, but this is the best that we can do, and we continuously find ways to improve this process.

Alex talked about the limited data on GAMT, and so I'm not going to highlight any of that, and I just wanted to put this out there, which is a very important point to make, that there is great -- as much as there is harmonization in newborn screening programs, when it comes to implementation of a new condition, that implementation cannot be generalizable, especially from other programs that are screening for that particular condition. They learn quite a bit from them, but once they experienced it, it is not the same in other states. Next slide.

Quick summary, next slide.

Approximately half of the states reported that it would take two or three years to implement GAMT as part of the newborn screening programs after they have the authority to screen for GAMT. Their readiness, as I highlighted, or I tried to highlight, varies across the country in that 35 percent of states reported that they can implement or are able to implement GAMT testing within two years and then another 20 percent said that it would take them about three years to implement GAMT. Next slide. Can you go back one?

Thank you for Utah and New York for sharing your experiences of screening for GAMT and certainly being able to highlight how with the successes and challenges, you've been able to do that.

We cannot dismiss all of the activities that has gone on to validating GAMT in the state of Michigan for the last three years, but throughout the process, they still continue to at least find ways to figure out how to be

able to move forward to screen GAMT.

And I've highlighted this a number of times, but the an FDA-approved kit certainly doesn't hurt in the process of adding a new condition, in this case GAMT, to state newborn screening programs to facilitate the process. Next slide, please.

The ability to multiplex is a plus, plus for sure in that it's mass spec and, at least for the LDTs, states that are using LDTs, they seem to have been able to bring that on with time, but an effort. But they were able to do that for population screening in their states and that states have eliminated successfully the second-tier testing for GAMT. I think that is a major lesson learned from the two states that are screening for GAMT.

Challenges still remain the same, validating the test, funding, not just for the newborn screening program, but all of the system-related activities, staffing, and then competing priorities, and I think that's my final slide.

Next slide, please.

I think that is it. So, thank you.

CYNTHIA POWELL: Thank you, Mr. Ojodu, and thank you, Dr. Prosser and Dr. Kemper.

Before we move onto our question-and-answer period, Dr. Kemper, did you have any final remarks that you wanted to make, or should we just go on?

ALEX KEMPER: We're happy to entertain questions.

CYNTHIA POWELL: Okay. Thank you. So, we'll open this up for discussion. Committee members will discuss first, followed by organizational representatives. Please use the raised hand feature and also speak your first and last names each time you ask a question or provide comments. Melissa Parisi.

MELISSA PARISI: Hello and thank you. This is Melissa Parisi from NIH, and I appreciate all the thoughtful presentations and all of the important data that you all shared.

I have a question about the "other"

category and those infants that were initially screened positive but for which we were unable to confirm the diagnosis and may have had an off-target condition, and I'm just wondering if there -- and maybe this is a general question for our metabolic genetics friends -- if there are any other conditions that we think may be occasionally picked up by this assay that, for whatever reason, either are not -- we don't know what it is, or they have not been well described, or if there are some additional sort of secondary conditions that may be picked up by the GAMT screening process.

ALEX KEMPER: Let me first take a stab at that and then then I'll open it up to others. We did ask the Technical Expert Panel about that particular question. Again, the only "other" conditions being picked up thus far through newborn screening that we're aware of is that one case of arginase deficiency.

The other thing that we lumped into that "other" category because, you know, it's

sort of unclear how you handle it, are the newborns who were referred, but who died prior to diagnostic evaluation. We didn't want to count them as lost to follow-up, because it wasn't really, you know, like the typical system lost to follow-up. But we did want to keep track of them. So, we lumped them together in that "other" category and from what we understand, it's likely that those were sick babies in the NICU and that's what led to them having that positive screening in the first place.

But to get back to your sort of broader metabolic question, it's only arginase deficiency where the Technical Expert Panel didn't think that there would be other off-target things that would be picked up and I'll just leave it there.

CYNTHIA POWELL: Scott Shone. I think you're muted.

SCOTT SHONE: Sorry. Yeah, sorry. I hit the wrong button still and we've got three years into this. So, a couple of questions. One

for, I guess, Jelili and one for Alex.

So, Alex, one question about the treatment, because in the text of the report -- and it didn't really jive or maybe I missed it on the slide -- is in the text, you said that their review did not identify any treatment recommendations endorsed by national specialty groups and I went back and looked at some of the previous evidence reviews and at least the ones I looked at all had some level, even MPS II, you know, had -- had some -- some type of treatment that was endorsed by a national subspecialty group. So, I wanted to ask about, you know, can you help delve into that for me to understand a little better, as you know, I'm not a clinician, so help me understand that and two, and related, is the treatments are not pharmacological, they are dietary supplements and there was a flag in the review around the potential, because of the way the FDA class, that they can be changed, but ACD has negotiated a, I guess, a partnership to produce higher-quality supplements and I'm

wondering, given the challenges we're seeing right now that don't seem to be ending on supply chain and issues like that, how -- how is that balanced on a dietary supplement classification versus the support for a pharmacologic, and availability of an unchanging therapy that the -- that patients can rely on, so?

ALEX KEMPER: Yeah, let me -- so, let me first touch and see if I can talk about the endorsed treatment guidelines. We didn't find, you know, any national society that had endorsed the specific treatment parameters for GAMT deficiency. What we did find is a number of articles that suggested ranges of the different therapies and then there was recently a book chapter that sort of brought it all together and, you know, lined up what the treatment recommendations are, including the specific dose ranges of the medications. You know, I don't know why there's not, you know, like, society recommendation for treatment, and I suspect some of that has to do with the rarity of the

condition and the fact that there's general agreement amongst the, you know, small number of subspecialists that take care of these children about what the right dosing ought to be. So, I'm just not sure why they haven't taken it to the next step, but I don't want to leave with the impression that people are sort of all over the map in terms of where they -- they treat those. There does seem to be consensus across the articles that we read and then that book chapter that I think is probably the closest to the definitive thing. So, that's thing one.

Thing two, you know, anybody can order creatine from, you know, amazon.com right? You know, in fact, we see, you know, teens who want to, you know, bulk up who buy creatine that way. I think the Association for Creatine Disorders was wise in terms of recognizing that the prevalence of those supplements, you know, might be suspect, and so they've contracted with a -- with a lab that met, you know, their criteria for getting the creatine and the

ornithine. What we were told by them and by the Technical Expert Panel is that you can get sodium benzoate fairly easily from a compounding pharmacist and, as a matter of fact, the volume that you get you when you go there is so much greater than anything that any like newborn would need. It's like a huge supply of it. So, that -- that's sort of where that comes.

So, your other question, though, is about like, you know, what -- what's going to happen with the supply chain, and do we need to worry about the availability of therapy and, I mean, I can't predict, you know, what's going to happen in the future. But, you know, it seems like the supply is okay now based on what we were told in our interview with the Association for Creatine Disorders or Deficiencies, I should say rather.

SCOTT SHONE: Now, it's just why you unmuted it. In terms of, you know, we've often talked about, particularly with that much higher dollar therapies, gene therapy, et cetera, equity

and access issues. I -- is it safe to assume or not even assume, but can you -- would you find that, based on what you just explained with ACD and everything, that they -- that those issues in terms of equity and access are somewhat easier with this type of therapy or similar despite the less --

ALEX KEMPER: Well, I would say -- so, it's not within our purview to figure out like what the costs of therapy are because, you know, we just can't do that in the time that we have, but I'm looking right now, that's why you're looking at the side of my face, at a sheet that the Association of Creatine Disorders put together in terms of the monthly cost and, of course, the monthly cost depends on -- on how much you weigh but can range anywhere from like $30 a month for the smallest child to about $130 a month for like a full sized, you know, starting in late adolescence through -- through adulthood.

So, the, you know, that's obviously a lot less than gene therapy, but there are

issues, right, because of the way that the, you know, the supplements are covered that individuals might have to bear the cost. Of course, you have to weigh that with the costs of therapy if you're not treated early, if you believe that early treatment leads to better health outcomes. So, you know, I just -- it's just sort of that weighing thing.

But, you know, we've talked in this group many times about the challenges of medical foods and supplements for these conditions, which, you know, sort of goes beyond what I could do.

The other thing, I guess I should point out -- sorry, I know I'm giving you a long-winded answer, but it's my last chance today to answer questions for you in this format, so I want to make sure I can take full advantage of it -- is these are not like, you know, little supplements like somebody might want to take, you know, to -- to bulk up or whatever, I mean, these are, you know, these are specific doses that are

applied to treat a specific condition. So, I just don't want to confuse like taking a little supplement versus using it really as a medication.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Thank you. I am putting on my hat as a biochemical geneticist to respond to a couple of -- to respond to Dr. Parisi's question. I think specifically that the question was about what other conditions might be identified by this. Arginase deficiency is the one that Dr. Kemper mentioned, and that is one for which is currently a secondary. It's on the secondary screening list and actually would be highly desirable to have improved newborn screening for that and it's entirely possible that this -- that the addition of guanidinoacetate would improve our ability to diagnose arginase deficiency in a timely fashion, which would have very real benefits for those individuals as well, who are now not routinely or reliably identified by newborn screening.

There's also some question of whether other of the distal defects may be better identified, which are also secondary targets or where -- that might be better identified by having a secondary flag or a secondary metabolite to monitor.

And the last thing that I don't think we really have discussed is that GAMT deficiency is one of three creatine deficiency disorders and the other two are not screened right now and there would be benefit to those patients for screening as well. Guanidinoacetate has potential to have low values, have potential, along with low creatine to be a marker AGAT deficiency, the first step in that pathway, which would also be very, very beneficial to those rare patients, because they would also benefit from early identification and therapy.

So, from the -- from the secondary -- the secondary conditions would all -- unlike many of the secondary conditions from other primary RUSP components, where there's no

treatment, so it's sort of unfortunate that you pick them up, I can't think of anything that wouldn't be good to identify with this test. So, that's actually kind of an added bonus, from my perspective.

And then, if I may, to Dr. Shone and Dr. Kemper's comments about dietary supplements, I know that the FDA defines dietary supplements as a compound that its unaltered form is a component of foods that we take in. But I think it's really clear that we -- that we recognize these are not dietary supplements. These are small molecules that are given to modulate the output of a biochemical pathway in an individual with a severe genetic disorder and they are treatments, and we need to continue to work with the community, with the FDA, and others to more carefully define how these molecules are described and get away from this dichotomy of pharmaceutical versus dietary supplement, because it does a great disservice to many individuals with rare diseases.

CYNTHIA POWELL: Thank you. Robert Ostrander.

ROBERT OSTRANDER: Thank you. I just want to sort of expand on what Shawn just said. For a while, a few years ago, we on the Advisory Committee and other groups that I belong to, had made a big push to chime in on the fact that medical foods needed to be considered disease treatments and therefore covered by the mandates from the Affordable Care Act, et cetera, and that has not been a big topic for the past few years. I did some advocacy of the American Academy of Family Physicians about it, I think it was five or six years ago, and, you know, it's now officially the position of the Academy. But I don't think any real advocacy has happened around that. I don't know to what extent the Advisory Committee in the report of the Secretary can advocate for that. But I think, you know, being even more specific that we need to distinguish the two is, we distinguish the two and insist that they be covered similar to

pharmaceuticals for treatment of medical conditions.

CYNTHIA POWELL: Thank you for your comment. I'm not sure of the current status. I know in the past, bills have gotten stuck in Congress and not passed to support coverage for medical foods for patients with inborne errors. I know we have a young girl in North Carolina riding her motorcycle around the country to raise money for families whose children have inborne errors of metabolism and can't afford their low-protein foods. So, where the state provides formula, they do not provide funding for low-protein foods and those are extremely expensive, if any of you have tried to buy those in the grocery store or ordered them. So, certainly a need that we shouldn't forget about despite frustration that it has not gone anywhere in the past. So, Scott Shone.

SCOTT SHONE: All right. So, I just want -- two things. One, I just to be clear that I wasn't taught actually talking about costs. I

just wanted to make sure that babies identify what some level have access to these -- to these -- what I think the evidence review has shown, is to be of extreme benefit to the people -- the children that are identified. So, I -- I was -- I didn't want to delve down into health care costs, so I wasn't trying to derail a harms and benefits discussion and just want to be clear about my intention there is making sure that everybody can have access to clearly what's benefited, particularly the families that we've seen on the multiple calls over the last few years.

But, I did want to go back to -- I was going to ask Jelili a question and I don't know if Jelili is still on or if this is going to go to Alex, but I think the Michigan experience is a little -- it's not even a little, it's -- it's somewhat concerning with the three- to four-year attempts at trying to validate and come off of an FDA-cleared kit, because I think it's important for everybody to realize that if you

modify an FDA-cleared kit, it's now a laboratory-developed test and most states -- let me back up, I won't say most. I tried to look on New Steps for some actual data to support this. So, I don't want to get into the numbers, but many states are now using FDA-cleared kits. North Carolina transitioned last year. So, we don't want to go back to modifying and so I'm trying to understand and learn from our colleagues. I think it's going to be -- I think that that's -- and I've been getting texts during the call, yeah, in the Public Health System Impact, we put that as a barrier. I think that's really going to be -- the potential barrier on the timeline for this is figuring out the best way from a regulatory standpoint for labs to stand this up. I've heard the cost; I've heard the therapy. I think that, unlike some of the other things where it's not as big of a gap, I just, I worry -- I just worry about Michigan's experience and the scope of it because clearly New York and Utah figured this out with their LDTs. But I think

there's some more there and I don't know Jelili, if you can comment on exactly what -- I mean, there was sensitivity and instrumentation, but not everybody's going to be able to upgrade say, you know, two to six tandem mass specs at $350,000 apiece. That changes the dollar estimate that was portrayed.

ALEX KEMPER: I don't see Jeleli right now. So, maybe I'll just fill in and just add that that I think, you know, you summarized the issue nicely in terms of laboratory-developed tests versus using an existing testing kit and, you know, Michigan did talk about, you know, potentially needing to update their older tandem mass spec devices, which again goes sort of outside of my area.

One thing that we're not able to comment on for the -- for the evidence review is what manufacturers of testing kits plan to do in the future. So, if this moves forward, you know, presumably they'll have an incentive to develop a testing kit that would then be available to

anybody who's interested. But I'm not sure what that process is, can't comment on the timeline, or what its potential cost would be.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Thanks. Dr. Shone, thank you for reminding me of the other thing I wanted to say in response to your comments about the supply chain issues. In addition to the -- it turns out, there are a number of suppliers that metabolic providers have found to be reliable for these supplements and for these products, these dietary or these nutrition or these treatments that we use. But the problem is that because they're not FDA -- there's no FDA oversight of their production. In addition to the problem of whether they're reliable, we can find that out by experience or private testing, but what we can't find out is, where does it come from. So, if there's suppliers of creatine that we use routinely, are they all getting their supply from the same producer, and we don't have any way to know that

or understand that. That said, if past experiences in the example, supply chain issues are more likely to be a problem with pipette tips for the newborn screening labs than they are for access to creatine.

CYNTHIA POWELL: Thank you. Any other questions or comments before we move ahead? All right. Thank you again for the evidence review. For each condition considered for full Evidence-Based review, two Committee members are selected to serve as liaisons to the ERG. These Committee members are tasked with developing a report summarizing evidence review, forming a recommendation for the condition rating and overall Committee recommendation, and assisting the chair in leading Committee discussion. Before turning it over to Dr. Jean DeLuca and Dr. Shawn McCandless, I want to give a very brief overview of the decision matrix.

The Advisory Committee first assesses the magnitude of net benefit and then the certainty about the evidence. After this

assessment, readiness and feasibility from a State Public Health Program perspective are assessed. This two-step decision process is used to guide the Advisory Committee recommendations to assure clarity and transparency. The Advisory Committee assigns codes in this process, which are then used in the development of recommendations.

The Advisory Committee adheres to the following principles in developing recommendations; that the recommendations are evidence-based, there must be scientific evidence that screening leads to improved outcomes, and that these benefits outweigh the harms of screening, and the outcomes that matter most are the health benefits to individuals screened. The overarching goal of screening is to improve the health-related quality of life of newborns. Next slide.

So, as you see here, the magnitude of net benefit from substantial to negative and then the certainty of that net benefit from high

to moderate to low is the basis for that -- that rating score A through L. Next slide, please.

Recommendations take into account the readiness of State Public Health Systems to begin comprehensive screening and the feasibility of either beginning such activities or developing the ability to do so. Readiness assesses the current ability to implement comprehensive screening and feasibility assesses the resource needs for effective comprehensive screening, including a general estimate of costs to adopt screening for the condition under consideration. Next slide.

And so, the feasibility ranges from high to moderate to low and then readiness of ready, developmental meaning that most State Public Health Departments have developmental readiness and screening has high to moderate feasibility, or unprepared, that most State Public Health Departments are unprepared to begin comprehensive screening and screening has high to moderate feasibility or a 4 rating that

implementation of screening for the targeted condition has low feasibility. Next slide.

Using as part of the matrix the Advisory Committee assigns one code to rate the evidence. So, an A rating, again indicating that there is high certainty that adoption of screening for the targeted condition would lead to a significant or substantial net benefit; B, there is moderate certainty that adoption of screening for the targeted condition would lead to a significant or substantial net benefit; C, there is high or moderate certainty that adoption of screening for the targeted condition would lead to a small to zero net benefit; and the D rating, there is high or moderate certainty that adoption of screening for the targeted condition would lead to a negative net benefit; or an L rating, there is low certainty regarding the net benefit from screening. Next slide.

So, once each of the readiness and feasibility ratings are assigned, the Advisory Committee uses the Public Health Capacity Matrix

to assign readiness and feasibility, and I've already gone through those -- those ratings.

So, are there any questions about the decision matrix? All right.

Before introducing Dr. DeLuca and Dr. McCandless, I'll remind organizational representatives that unless otherwise directed, the deliberation that follows this presentation will be for Committee members only.

Dr. Jane DeLuca is an Associate Professor and has been at the School of Nursing at Clemson University South Carolina since 2012. She has a clinical appointment at the Greenwood Genetic Center in the Metabolic Clinic caring for newborn screening patients and others with inborne errors of metabolism.

Dr. DeLuca has worked in newborn screening as a nurse practitioner since 1999. Her research interests include parents' and families' experiences of newborn screening.

Dr. Shawn McCandless is Professor of Pediatrics and Section Head for Genetics and

Metabolism at the University of Colorado, Denver School of Medicine and Children's Hospital Colorado.

He is a past President of the Society for Inherited Metabolic Disorders. He served on the Ohio Department of Health Newborn Screening Advisory Council for twelve years prior to moving to Colorado.

His research is focused on inborne errors of metabolism and Prader Willi Syndrome. He is a fellow of the American College of Medical Genetics and is active in the SIMD and the American Society for Human Genetics.

And I'll now turn it over to Shawn.

COMMITTEE REPORT: NEWBORN SCREENING FOR GAMT DEFICIENCY

SHAWN MCCANDLESS: Thank you, Dr. Powell, and I want to thank -- also thank Dr. Powell for her assistance with this -- with the work that we're about to present that Dr. DeLuca and I, along with guidance from Dr. Powell, have put together to sort of frame the discussion.

May I have the next slide, please.

To frame the evidence that you've heard already into the -- into how we -- we might want to think about it, as it applies to the decision matrix and just a couple of things that I want to point out to supplement what Dr. Powell said about the decision matrix is that the first is that, for the purposes of this presentation we are -- we are certainly referring to understanding the level of certainty of net benefits of compulsory population-based newborn screening, and you've heard me use that term before, but I think it's important that we keep coming back to the fact that this is a Public Health Program that is mandated for all newborns and that people don't have a choice about, and so it -- it requires a high bar for adding conditions and it considers -- it forces us to consider both the benefit to individuals who were affected, which is very important, but also the -- it requires us to consider benefits and harms to individuals who are not affected, but may have

a positive screen or may have it be a missed case.

The second component feasibility of newborn screening is feasibility in the world in which we live, not in the world in which we wish we lived, for the purposes of this discussion.

And state's readiness to implement newborn screening refers at least in my mind, refers to the newborn screening laboratory, the newborn screening program, as well as the availability and access to follow up care and appropriate treatment. May I have the next slide, please? And you can go on to the next slide.

Just a reminder that what Dr. Kemper has told us about guanidinoacetate methyltransferase, it is an autosomal recessive disorder of creatine biosynthesis. It's one of three disorders that lead to cerebral creatine deficiency. The most common is cerebral creatine transporter that's X-linked, so primarily affects males and for which no screening method has yet

been identified. Also, treatment is much more difficult for this condition.

And then the arginine glycine amidinotransferase deficiency or AGAT, is also rare. There's -- it's so rare that we don't really even have a good estimate of birth prevalence. But again, because guanidinoacetate does not accumulate in that condition, it would not be detected by this -- by high levels of guanidinoacetate, although, as I mentioned earlier, low levels could potentially eventually lead to screening for that condition, which would also be beneficial because those children benefit from treatment with creatine as well.

The neurological deterioration, just to remind you, begins early in infancy and it is hypothesized that the decreased CNS creatine is the primary factor. That also that there's a toxic effect of the accumulation of guanidinoacetate, evidence supporting -- it's hard -- it's hard to be overly certain or confident about which of those two things is most

important, and I would just say that, from the reading I've done, that the association -- individuals that have AGAT deficiency can also have some of the same problems. There's no finding in GAMT deficiency that you -- that has not been described also in AGAT or creatine transporter defect. So, it's a little bit tricky to say this is guanidinoacetate causes this, low creatine causes this. But what we do know is that the combination is not good.

We've heard that there are several -- that there are a variety of DNA variants that have been described. There's only one gene that's associated with this, but that gene can have many different variants and there are many that are undescribed, and probably more than half are what we call private or very rare and not sort of prevalent in a particular population. Although there are one or two that have been shown to be somewhat more prevalent and then the birth prevalence you've seen, based on the newborn screening programs in New York and Utah,

which are right on the order. The most likely number is about 1 in 500,000, but that could range from much less than that to perhaps as high as 1 in 140,000 births. May I have the next slide, please?

The clinical symptoms you've heard about, the onset of symptoms is often described retrospectively to have been noticeable at 3 to 6 months, sometimes as late as 2 years. With that said, the clinical data -- the literature is very clear that clinical diagnosis is often delayed and can range from the neonatal period, if there's a family history, to well into adulthood, and the neurocognitive outcomes are poor.

There -- there is variability as there is with every genetic disorder, but untreated neurocognitive outcomes are poor.

The findings are somewhat nonspecific, which is the likely explanation for the typical delay in getting to the diagnosis clinically and unfortunately, as you've heard already, the majority of individuals who are

identified clinically, at least up until now, are -- have permanent brain injury by the time of diagnosis is made.

And then, as Dr. Kemper noted, life expectancy may be limited due to complications, but it's not clear that the underlying disease process limits lifespan, nor is it clear whether there's -- whether people continue to have neurodegeneration over time. At least, it's not clear to me. May I have the next slide, please?

Just a couple of points about screening and the confirmatory diagnosis. The population-based screening you've heard about, I think it's important to point out that Utah uses an un-derivatized method and New York uses a derivatized method for measuring guanidinoacetate and creatine. And the importance of that is that those are the two important sort of dichotomous points for the existing mass spec screening programs across the country. So, every state can do -- some states do un-derivatized, some states do derivatized. Regardless, a lab that using

those methods should be able to add this with some effort, but it shouldn't require starting over from scratch with their entire process, at least in regards to derivatization.

The other thing to point out is that both of those programs have determined that the primary screen has so few reports, that a second-tier test is probably not necessary, and that neither one of them is currently using a second-tier test.

Mr. Ojodu told us that maybe half of labs would think that have not started think that a secondary -- a second-tier test would be necessary, but experience suggests that that may not be the case.

And then, the definition of an abnormal screening test is guanidinoacetate and guanidinoacetate to creatine ratio that are above a cutoff value.

Method development and validation, as Mr. Ojodu told us, is quite variable from state to state and currently there are no FDA-

approved kits available. But, as Dr. Kemper mentioned that there is certainly possible that existing kits could be modified -- existing FDA kits could be modified to without probably too much trouble to create an FDA-approved kit in the future, but that is not currently available.

And then the final point to make about -- around confirmatory testing is that while most people feel like they know how to identify GAMT deficiency, we've not been able to identify a consensus case definition that would be necessary for long-term follow-up programs to use for their data collection. It does seem to a clinician that this is not a difficult diagnosis to make if you know to look for it.

The other thing to point out is that the diagnostic testing should use plasma and not urine, as there has been -- it has been shown that urinary guanidinoacetate concentrations are quite variable and can lead to missed cases. So, that should not be used as the diagnostic test.

And then genetic analysis is

strongly supportive of the diagnosis and there may be times where it is necessary, although it is likely that many cases can be confidently treated without having or waiting for molecular test results to come back. May I have the next slide, please?

Just to remind you, the treatments that are available, there's two primary focuses. One is to replace central nervous system creatine by giving creatine supplements and that has been shown to -- or that is thought to be effective.

And the second is to try to minimize the production of this presumed toxic molecule guanidinoacetate or guanidino acidic acid by doing a couple of things. Number one, you give ornithine, which because it's an enzymatic -- this is an enzymatic reaction that makes ornithine and guanidinoacetate. If you have high levels of both of the products, that should tend to slow or reduce the flow through that enzyme. So, by giving ornithine, you are providing product inhibition of the enzyme.

By minimizing arginine by dietary restriction, you are minimizing the substrate for the enzyme, which should also slow the enzyme activity and finally, benzoic acid pulls glycine -- benzoic acid gets -- binds to glycine to make something hippuric acid that's excreted in the urine. So, again you're reducing glycine by giving benzoate, reducing arginine by limiting protein in the diet, and then replacing ornithine and guanidinoacetate is already high. So, all of that should tend to push this reaction away from making more guanidinoacetate.

I think it's worth pointing out that there is no literature -- there’s really not compelling literature that defines the magnitude of the effect of any of these treatments. May I have the next slide, please?

And that really reflects, I think, several things. The fact that this is an ultra-rare disease and also points to this is one of many reasons that the rare disease community, of which I am part, we have to do a better job of

defining outcomes and defining treatments for these conditions to help our families who are -- and advocates who are nominating conditions. We need better data than what we have, and this is a great example of that. Partly, we don't have the data because it's very rare but partly we don't have the data because the publications that have -- the publications were not as good as they might have been, or could have been if people in the rare disease community, like myself, were more thoughtful about what we're trying to accomplish when we publish these papers.

In terms of the -- again there's no formal treatment guidelines published -- there are expert opinions published. The care team for an individual affected is primarily defined by those individuals that have abnormal neurological development. And so, with newborn screening, it's likely that what you -- that probably the needs for follow-up would be based on what a healthy child would need and you would respond to any symptoms that arose in terms of standardized

monitoring and screening. You would definitely need to have a team that's including a dietitian who's familiar with the use of therapies and a protein-restricted diet and how to do that safely.

But then everything else is going to probably be based on the -- on the symptoms that the individual develops. There is periodic screening for guanidinoacetate that is recommended and creatine. The use of MRS as a monitoring tool to show normalization of central nervous system. Creatine has not been demonstrated but has not -- but has been not demonstrated either. We just don't know.

And finally, I don't think we've mentioned this, but high doses of creatine in weightlifters have been associated on occasion rarely with kidney injury. And so, there is a recommendation for monitoring of kidney function to minimize the risk of injury to the kidneys from the therapy and gene therapy and other potential therapies are very early in development

and probably not -- should not impact the decision at this time. May I have the next slide, please?

So, putting it together, the benefit to affected infants and children. The benefit to individuals with GAMT deficiency based on a very, very limited literature that showed that older siblings diagnosed clinically all had developmental issues that range from mild to severe but mostly are moderate to severe, and I think that Ms. Wallis' family that we saw earlier, is a very good example of what one would expect to see in families that have GAMT deficiency. So, even though that's a single anecdote, I think it is likely reflective of what the literature and the expert opinion together have a belief to be true.

I want to talk about the case reports of the 8 younger siblings who were identified because of an older sibling and treated before 6 months of age; 7 of the 8 are reported to have normal development. Almost all

of those that were not even a year old at the time the report was published. So, we don't have long-term developmental data on those individuals, and it would be very, very helpful to have that.

However, the 7 of 8 that had what was reported to be completely normal development, even though there was no standardized approach to assessing that development, is very -- does point very strongly to the benefit of treatment. The 1 infant that was described who was treated at 8 days of life and at 11 months of age, was noted to have hypotonia and developmental delays. The implication could be that that the treatment is not 100% effective. It could be, as the author speculated in that paper, that maybe the treatment was not applied. But the other thing I think it's important to point out from these kinds of case reports is that that those children -- that both siblings were homozygous for the same mutation, which raises the question in that family whether there may have been other genetic

factors that were shared by the parents that are contributing to the developmental outcome in those children. And one small piece of evidence to support that possibility is that in the older sibling, there were some MRI findings that have not been typically described in GAMT deficiency. So, while that 1 out of the 8 cases is -- does cause us to be careful to not overstate the value of treatment, I think it's also possible that there are other factors in that case, and I don't consider that a significant -- a significant sort of question mark about the effectiveness of therapy from my perspective. May I have the next slide, please?

So again, we think that reasonable assertions based on the limited data or that pre-symptomatic therapy is most often associated with normal neurologic development. Treatment is likely associated with better neurological outcomes, even in children identified late, in terms of cognitive development and function and that both of those should correlate with improved

quality of life, although we do not have available to us quality of life data to prove that.

And, in summary, it appears that earlier initiation of treatment likely maximizes benefits of therapy, whether that is pre-symptomatic or after symptoms have developed. The sooner treatment starts, the better. Pre-symptomatic treatment appears to be best. May I have the next slide, please?

Potential harms of this are again primarily related to individuals that do not have GAMT deficiency. So, the rest of the population, false positives appeared to be a very low concern because there is very -- it appears to be reliable confirmatory testing that's widely available unlike some other conditions that we've discussed, there really don't appear to be indeterminate results. There are unlikely to be children who confirmatory testing can't determine whether they're affected or not. And so, that means that it's unlikely that anyone will be

treated who won't benefit from treatment.

The potential for being lost to follow-up is low. And really, the only -- even that "other" category, you know, if you have a different diagnosis that is flagged because of the guanidinoacetate testing, that's actually a positive. But those families in whom the baby dies before the abnormal newborn screening is found where there may not be the possibility of confirming the diagnosis, that is a potential harm that we don't want to completely disregard because those families will then not know whether they are -- whether they are at risk of having an affected child in the future. So, that is a very small, but potentially real potential harm.

And also, we just want to point out that the cost and burden of confirmatory testing for this condition is probably lower than for many other conditions on the panel. And so, that's also an important factor.

No false negatives have been reported.

And again, the lack of a clear case definition, I don't think is a major barrier or potential harm. May I have the next slide, please?

So, finally, I just want to walk through the projections that Dr. Prosser showed us based on 3.6 million births annually in the US, if we were to -- if GAMT screening were to be occurring in every state in the United States. We would expect to identify about 7 cases per year is the most likely number. It could be as low as 2, it could be as high as 18 based on the data we have available.

But that 1 out of -- so, 1 out of 13 infants with a positive screen will be diagnosed with GAMT deficiency, which means that 12 out of 13 will have some other explanation, one of which could be another thing, but more likely, these will be false positives and so that false positive -- it's not true -- the true false positive rate and the reason for that is that the false positive rate is extremely low for this

because the screening test is very good. And so, the total number of positive screens reported is very, very low. So, the false positive rate for all babies screened is going to be extremely low, but the rate of false positives among those who flag, who have a positive screening test is on the high end of what's currently -- if you look across the board at newborn screening conditions right now, the -- got the true -- the ratio of true positives to false positives is a little bit on the -- the ratio of false positives to true positives from the positive screens is a little bit higher than is typical, but still in the sort of the ballpark of what we have been thinking about recently for what's acceptable for newborn screening.

And I think I've already addressed the other two points there -- bullet points there. So, may I have the next slide?

I will turn the rest of this talk over to Dr. DeLuca.

JANE DELUCA: Thank you, Dr.

McCandless. I want to thank Dr. Kemper and Mr. Ojodu and Dr. Prosser for all their help in gathering and analyzing evidence and I also wanted to talk and just thank Dr. Powell for her leadership and help with preparing our presentation for the Committee.

So, we'll start with describing the issues and net benefit and balance of benefit and harms as it pertains to certainty about presenting the evidence. Now, we use this example here with the balancing stones structure. So, next slide, please.

One of the first things we thought about when it came to balance of benefit and harm that can occur within a broadly screened population is that is it possible to perceive benefits and harms that could include different persons within a population or a specific group.

Is there a group that is different, you know, within our population that may actually have more harms and more burden because of screening?

So, from the evidence we have, it doesn't appear that guanidinoacetate methyltransferase deficiency would affect one select group over another, you know, if no -- if there's international cases that have been identified.

However, we have small numbers of cases to draw from. So, it's possible. At this point, we just don't know. In the future, we may be able to have to think about this again and whether there are some specific characteristics, which bring a certain group to the forefront. Next slide, please.

So, is there a significant net benefit for compulsory population newborn screening. So, limited evidence suggests there is significant benefit for children who receive therapy early. Babies can incur substantial benefits by being treated early, that is treated pre-symptomatically. Treating before a diagnosis is secure or definitively made does not seem to be an issue for GAMT deficiency. The diagnostic

studies are accurate. So, there should be a low risk of harm for treating patients that do not need treatment. The treatment itself, diet, and medications are well known within the medical treatment world.

From the current evidence, it does not appear that indeterminate cases occur. There appears to be a low risk of potential harm for families for the status of classification that's a company by prolonged monitoring when there's no diagnosis.

The diagnostic studies are reliable. That is not to say that if widespread GAMT screening is adopted, that an indeterminate case may be identified with mildly out of range creatine or guanidinoacetate levels, which would need to be addressed in the future.

So, for net benefit and certainty, it came down to two possibilities, high certainty of significant benefit. There is a high certainty of significant benefit that would occur or moderate certainty of significant benefits,

and if they're moderate certainty, that's significant -- the screening would have significant benefits. Next slide, please.

So, we made the decision that the existing evidence for guanidinoacetate methyltransferase, the designation that fits best is moderate certainty. The available evidence is deemed sufficiently compelling to determine the effects of early detection and treatment of newborn babies and on targeted health outcomes. But confidence in the evidence was hampered by a number of factors.

These estimated constraining factors or basically the evidence is the number of studies, the quality of the studies, study quantity, quality is not robust, and consists primarily of case studies and expert opinion.

There are moderate limitations in terms of evidence being able to be general generalizable for early detection to newborn screening.

So, the designated choice of B is

because the data is limited and largely based on expert opinion, but if it seems substantial, but the certainty is modest. Next screen -- next slide, please.

Newborn screening for GAMT deficiency feasibility and readiness. Newborn screening tests are available and appropriate for high throughput screening tests.

Most Public Health Departments would require 1 to 3 years to implement screening. So, we consider the development -- the readiness to be developmental. This could be even if resources were available because there could be potential barriers due to validating methods and refinements before a full screen implementation could occur. States may struggle with adding screening, so within a reasonable period of 1 to 3 years due to these challenges and methodology.

Clear case definition is needed, as Dr. McCandless stated. The proportion of true positive to all positive newborn screening results in the range of conditions occur on the

RUSP is founded.

In terms of feasibility, it is likely a moderate range of feasibility. Screening programs implementation is probably possible and within the financial limitations of most state health departments. Treatment costs for follow-up would be reasonable. Follow-up resources are thought to be mostly adequate to demand. Treatment is reasonable and within the range of other treatments that now exist for metabolic conditions.

Expansions may be needed for training and personnel, follow-up in unforeseen issues may also occur, and I'm thinking of the demands of the pandemic and pull on public health resources during those types of -- those types of times. So, next slide, please.

So, here is just a picture of the matrix in terms of our findings so far. We have a designation of B for significant benefit and moderate certainty. We have developmental readiness and moderate feasibility for GAMT

deficiency. Next slide, please.

So, newborn screen screening for GAMT meets the criteria for the matrix category B2. Developmental readiness for newborn screening programs to enact GAMT screening is developmental and that could be very varied across programs and most states could add MS/MS tandem mass spec approaches, but the lack of an FDA-approved kit increases time and cost implementation in terms of feasibility.

Now, the addition to the RUSP of GAMT may facilitate adding these metabolites to existing kits. Next slide, please.

So, we came to the conclusion that we recommend that GAMT deficiency should be added as a core condition to the RUSP.

What I'd like to do now is to open up discussion among the Advisory Committee members.

CYNTHIA POWELL: Thank you, Dr. DeLuca and Dr. McCandless and, yes, will now open it to Committee Member discussion.

COMMITTEE DISCUSSION

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: I don't have anything groundbreaking to say. But, I just think, you know, as we're moving into a vote, it's helpful to put on the record sort of what the members of the Committee are thinking. So, I agree with the classification of moderate evidence for significant benefit. I don't think the evidence is as strong as it could be, but on the other hand, I think it's probably as strong as could reasonably be expected for a condition with this level of rarity.

I think evidence from siblings is really quite compelling, you know, you get a lot of built-in control in that kind of comparison. So, I think that the sibling data is quite compelling. But I agree with the assessment that it really would have been ideal to have more formal developmental assessment of the, you know, of the siblings who have been reported.

So, yeah, I think everything else

seems to be in line with other conditions already on the RUSP and I recognize that it's going to take a while for many states to get this going.

But I think it's reasonable to add it to the recommendations and let the states work through that over the next couple of years.

CYNTHIA POWELL: Thank you. Scott Shone.

SCOTT SHONE: Thank you, Dr. Powell. I think -- I think, Dr. Brothers, you ended your statement with a perfect segue to what I want to say, which is that, you know, we've heard several times in the last few minutes, I guess last hour, around the challenges with getting this assay up and running and I think that that can't be overstated because, you know, we had a presentation earlier about the volume of RUSP alignment legislation that's sweeping across the country that requires states to add conditions within two to three years of them being on the RUSP and we just said, this is going to be a monumental challenge for states to do that. So,

we have a very big disconnect because this is not states not wanting to add it, this is a technical issue that needs to be worked out. We've said this is a developmental readiness.

So, I think that there needs -- you know, you have a state -- a strong state of Michigan who's been working on this doggedly to get this done and isn't. So, I do hope that the assertion that commercial vendors would want to pursue this comes to fruition. I worry that we're pinning -- like we're pinning on a RUSP approval that a vendor will -- will make an investment in something. But I do understand the finance of newborn screening.

I just want to say to Shawn and Jane, first of all, Jane, Happy National Nurse's Week. Thank you to you and your colleagues who take care of all of us, no matter whether it's newborns or beyond. So, thank you so much.

You know, I just felt like there was a lot of likely -- there's been throughout a lot of likelys, and insufficients, and to be

determineds in a lot of this, and I think, Kyle, you just really answered that of, you know, it's an ultra-rare condition and, you know, newborn screening will find that. It feels a little bit -- I'm not going to say it's research -- but it just feels like it's -- it's -- it's in that like where are we zone. So, I don't know if Jane or Shawn, if you can comment a little bit on any of that and particularly the state readiness and your thoughts juxtaposing that with these requirements -- legislative requirements that are going to be a big challenge. I think we need to acknowledge that, and I think that that, you know, that was teased out have been in the -- in the Public Health Systems Impact.

CYNTHIA POWELL: Jane or Shawn, would you like to comment?

SHAWN MCCANDLESS: No, thank you. I'm just kidding, Scott. That's obviously a tough question. But, I think that my opinion, as I've said before and anybody who knows me will know that I think that newborn screening

decisions about implementation, what should be screened, and what should not be screened, how state labs should operate, that should not be handled by legislative administrative assistants who are primarily the ones who are making the decisions right now. It's usually the incentives are not appropriate and what's driving those decisions is not appropriate and it's just not the right way to implement a compulsory population-based public health system It's just not and likewise to your point, you know, that I, as much as I like it, I think there's some -- there's something that's attractive about saying in a state, if the -- if this thoughtful process decides that this condition should be screened, that is -- that is reason enough for us to add it to our program. But to then not fund the work that needs to be done to make that happen and to not provide the resources that they need to make that happen and to not recognize that a legislative body is not equipped to set a deadline for when that should happen, at least

scientifically not equipped, that becomes very problematic, and I think that we really, you know, I don't think it should impact our decision making, but it should impact our advocacy as we're -- if we have opportunities to speak with our government affairs experts and with -- if we have opportunity to meet with legislators, we just need to educate them about the about the reality of this amazing program. It's amazing because of the hard work and effort that people -- that so many good people have put into it, but it's not amazing because somebody passed a law that said this needs to happen, and that actually has the risk of making things worse, not better, in my opinion. And that -- my opinion represents only my opinion. It does not represent HRSA, it does not represent anybody else on this Committee, it does not represent the institution I work for. It probably doesn't even represent my family's opinion, So, just going on record there.

CYNTHIA POWELL: Kellie Kelm.

KELLIE KELM: Yes, I wanted to tag a little bit onto what Scott just raised in terms of the test, you know, and the discussion of number one, obviously, you know, in many cases the issues with an FDA-cleared test, modifying a cleared test that a state has and then obviously Michigan struggling with their own development.

The only thing that I think is really interesting though, and I don't know if Jelili can speak to this or anybody else, is that the survey of the states for their readiness seemed to have matched a lot of the other ones that we've discussed in the last few years in terms of time. So, I didn't necessarily see a hesitation from states in that survey unless there was something in there that -- that -- some nuance that I was missing. But, I don't know if Jelili can speak to that or Scott or somebody else if I'm missing something, because the survey doesn't seem to capture, you know, that -- that concern. Thank you.

CYNTHIA POWELL: I don't know if

Jelili is still on or Alex, if you want to.

ALEX KEMPER: I mean, I -- I'll just comment that that your interpretation of the survey and the survey results were correct. What I'll say though is the people who run newborn screening programs are really kind of amazing, you know, heroes who, you know, sort of can do, you know, and want to take care of things. So, I think you always need to be a little cautious when you get information about how long they think it'll take them to adopt things. But otherwise, you're correct in terms of it is in line with other ones that we've done. Others, Jelili, maybe you can comment further.

JELILI OJODU: Yeah. Thank you, Dr. Kelm, for the question. There has been -- you are right. There wasn't anything particularly specific about this survey in comparison to other surveys that we've done. But there is a disconnect between when states say they're going to be able to bring on conditions and the reality of what happens. Again, you know, you can use

the last four conditions as examples of how long that it's taken for states to be able to bring on Pompe since 2015. I think there are about 30 states that screen for Pompe. SCID took 10 years for all states to be able to screen for it. MPS-I and X-ALD came on in 2016, and I think there are about 32 states screening for it. I mean, everything is relative. SMA was brought on in 2018 and about 42 states screen for it. So, we're trying to better understand the correlation between what they say in the state newborn screening programs, and, in fact, what happens in reality, and the reality is that it's -- it's different for all of the things that's caught, as Dr. Shawn mentioned earlier. Thanks.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: I'll just say that, thank you, Jelili, the difference is just what we're talking about, which is the power of the technological shift, right? So, the shift to SCID was the paradigm change took 10 years to implement across the country going to molecular,

but SMA was relatively easier, not easy, easier to add because it's just multiplexing on SCID. ALD, we needed to do second -- we needed to do second-tier. I mean, so that -- so, it is -- I'm just -- let me back up and just say these are somewhat caveats to the underlying issue here, which is that there is evidence presented of benefit of identifying these babies in the newborn period and that there is an effective therapy that can be applied that has evidence of positive outcomes, that there is benefit over harm. So, I'm going to say that clearly, right, because I don't -- I don't want to get derailed. But I just want to be clear that unlike -- unlike SMA, this is going to fall potentially like a SCID or something else that is going to take time while programs are working their doggedness to get it running. That's -- that's really my -- it's more of a statement than a criticism of the evidence review. I think the evidence review is good. Again, thank you to the team who did that.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Thank you and I don't -- I'm not -- I don't want to respond to what anything that Dr. Shone said. Actually, I'm changing the subject and so maybe if Dr. Cuthbert is going to respond to Scott, maybe we should let her go first.

CYNTHIA POWELL: Yes. Carla Cuthbert.

CARLA CUTHBERT: Yeah. I just wanted to -- to react just very, very, you know, I've been following this and I -- I largely agree with what most people are saying. I think that, you know, as we consider bringing on some of these new tests, we are always going to be faced with the is there -- is there an FDA-approved test and, if not, you're going to need to figure out how to do it on your own internally. So, if it's modification of an existing test, which is what some of the states may be facing, the difference between TREC and SCID and adding on SMA is that you're really only dealing with one small number, you know, the TREC biomarker and

its internal standard, whatever you are using there. But with -- with this platform, you're looking at a lot of biomarkers, and so there are a lot of things to keep track of and to make sure that you are now being responsible for all of those other biomarkers. So, that tends to be a little -- a lot trickier and, you know, in the case with Michigan and, you know, I don't specifically want to speak for them without them being here, but again, you know, if there is an interference, and I believe that they were using one transition, you know, they -- they were working at that, then tracking that, then there was a problem again and, you know, that -- that felt a bit iterative until they finally were able to use three different transitions and had a specific requirement to have them all be modified to make the call.

So, you know, it -- there are added levels of complexity when you're adding on or multiplexing with a very, very large test that has a lot of biomarkers.

So, this is the space that we're living in. It's not that, you know, we like this necessarily, but these are the real challenges whenever we are going to be called to add additional biomarkers. Thank you.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Thanks. I actually do want to -- I want to thank Dr. Cuthbert for that, because you raise a point that I don't think I've heard in this setting before and that is that multiplexing a test is great, but the more things you add, it gets harder and harder to add more things and at some point, it becomes asymptotic, right? You reach a point where you can't really add more to the test you're already doing by additional multiplexing. And I think that some of the data that we saw earlier from your colleague at the CDC sort of pointed towards that, where you start to have, you know, internal standards for one compound with fragments that overlap with diagnostic compounds for another condition.

You're going to reach a point we where you just -- you can't really multiplex -- you can't add more conditions or you can't add this condition, maybe this one -- this analyte will work, but this one won't. It's a really interesting concept, and it would be -- it'd be great if some -- if some scientist who is interested in newborn screening could do some modeling to give us, so that we can have some guidelines about sort of what would be realistic to expect.

Now, I will change the subject. I think this condition is really interesting. It gives a really interesting perspective on the sort of net benefit question, because when I think about other conditions that have been discussed, there are -- there's not a lot of data. But, it really -- what little bit of data there is and what the expert opinion tells us and clinical experience tells us is that the magnitude of the effect for affected individuals in this condition is very large, maybe bigger --

this is almost like PKU large maybe even better than PKU frankly, because the outcomes of PKU -- the long-term haven't been as great as we would like them to be.

It's also true that that may be true for GAMT deficiency as well. We don't know yet because we don't have data. But, that's okay. I think it's really interesting that we can end up with a recommendation of a B-2 for a variety of different reasons. Sometimes it's just that it really comes down to the evidence -- the lack of -- the lack of evidence, but it can also be that there's more variability in response to the treatment or that the response to treatment is partial, it's not complete. So, the net benefit is a really interesting question and I think it's sort of -- I think it would be valuable for this group to continue to do some fine-tuning to our matrix and our thinking about how we define the net benefit to just sort of really try to capture the nuance of, you know, in addition to the -- to the inadequacy of the data to capture the nuance

of the benefit to affected individuals of treatment and the magnitude of that benefit.

CYNTHIA POWELL: Thank you.

SHAWN MCCANDLESS: I'll stop there.

CYNTHIA POWELL: Any other comments or questions from the Committee? Okay, so hearing none, it's time for the Committee to move ahead with a motion. The motion would be whether to accept or not accept the recommendation both the rating and recommend or not to the Secretary. Anyone want to make a motion?

KYLE BROTHERS: This is Kyle Brothers. I move that we accept the recommendation to classify GAMT as B-2 and that we recommend to the Secretary that GAMT deficiency be added to the Recommended Uniform Screening Panel.

CYNTHIA POWELL: Is there a second?

SHAWN MCCANDLESS: This is Shawn McCandless. Oh sorry, go ahead.

JANE DELUCA: I second the motion.

CYNTHIA POWELL: Okay.

SHAWN MCCANDLESS: Kyle, this is Shawn McCandless. May I add to that, with the recommendation being that it be added as a primary condition to the Recommended Uniform Screening Panel.

KYLE BROTHERS: Thank you, yes.

SCOTT SHONE: I think you mean core, right? Core condition?

CYNTHIA POWELL: Yeah, core condition would be the working. Thank you.

SHAWN MCCANDLESS: Thank you.

CYNTHIA POWELL: Any additional comments, before we vote? All right. So, we're voting on the motion to accept the B-2 rating and to recommend that GAMT be recommended for addition to the RUSP as a core condition and this recommendation would go to the Secretary.

I'll now read through the members of the Committee. Please state -- if you are in favor of the motion, please state in favor. If you're not in favor of the motion, please state not in favor, and also let us know if you need to

abstain.

And I'm also supposed to ask does any Committee member have a conflict of interest regarding this vote and the need to recuse themselves?

Okay, Kyle Brothers.

KYLE BROTHERS: In favor.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: In favor.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: In favor.

CYNTHIA POWELL: Kellie Kelm.

KELLIE KELM: In favor.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: In favor.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: In favor.

CYNTHIA POWELL: Kamila Mistry, I believe, is still not available. Melissa Parisi.

MELISSA PARISI: In favor.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: In favor.

CYNTHIA POWELL: Cynthia Powell, I vote in favor. Scott Shone.

SCOTT SHONE: In favor.

CYNTHIA POWELL: Michael Warren.

MICHAEL WARREN: In favor.

CYNTHIA POWELL: The Committee has voted in favor of recommending adding GAMT deficiency to the RUSP. I will prepare a letter for the Secretary with the recommendation from the Advisory Committee.

Please remember that the Secretary makes the final decision on whether or not to accept the Committee's recommendation. This decision will be posted on the Committee's website.

I would like to thank everyone involved in the nomination, Evidence-Based review, and decision-making process, including members of the Committee, the Expert Review Group, and the Technical Expert Panel -- I'm sorry, the Evidence Review Group and the

Technical Expert Panel.

Thank you all and that ends day one of our meeting. We'll reconvene tomorrow at 10 a.m. Eastern time. See you then.

[Whereupon the meeting was adjourned.]