The Advisory Committee on

Heritable Disorders in Newborns and Children

U.S. Department of Health and Human Services

Virtual Meeting

Day 1

Thursday, February 10, 2022

10:00 a.m.

Attended Via Webinar

COMMITTEE MEMBERS

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Endowed Chair of Pediatric Clinical and Translational Research
Associate Professor of Pediatrics University of Louisville School of Medicine

Jane DeLuca, PhD, RN
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Professor of Child Neurology, University of Wisconsin School of Medicine & Public Health

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Director, Division of Human Genetics
Department of Pediatrics
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Scott Shone, PhD, HCLD (ABB)
Director
North Carolina State Laboratory of Public Health

Ex-Officio Members

Agency for Healthcare Research & Quality

Kamila B. Mistry, PhD, MPH

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Organizational Representatives

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Shakira Henderson, PhD, DNP, MS, MPH, RNCHIC, IBCLC
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Department of Defense

Jacob Hogue, MD
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Genetic Alliance

Natasha F. Bonhomme
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March of Dimes

Siobhan Dolan, MD, MPH
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National Society of Genetic Counselors

Cate Walsh Vockley, MS, CGC

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Society of Inherited Metabolic Disorders

Gerard Berry, MD, FFACMG

Director, Metabolism Program

Harvey Levy Chair in Metabolism

Professor of Pediatrics

C O N T E N T S

P R O C E E D I N G S

WELCOME AND ROLL CALL

[recording started a few minutes late, began during roll call]

CYNTHIA POWELL: New Committee member Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Here

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

SCOTT SHONE: Here.

CYNTHIA POWELL: Next, we'll take the roll for our organizational representatives from the American Academy of Family Physicians, Robert Ostrander.

ROBERT OSTRANDER: Present.

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

From the American College of Medical Genetics and Genomics, Maximilian Muenke

MAXIMILIAN MUENKE: Here.

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

STEVEN RALSTON: Morning, I'm here.

CYNTHIA POWELL: From the Association of Maternal of Child Health Programs, Sabra Anckner,

SABRA ANCKNER: Here.

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

SUSAN TANKSLEY: I'm here.

CYNTHIA POWELL: Is there anyone from the Association of State and Territorial Health Officials present today? We will have a new representative from them, hopefully by the next meeting.

We will not have Shakira Henderson AWHONN Group joining us today. And -- I'm sorry, was there -- did I miss someone?

DEBRA FREEDENBERG: Hi, this is Debbie Freedenberg.

CYNTHIA POWELL: Okay, hi, Deb. Thank you.

And we will also be having a new representative from the Child Neurology Society hopefully by the time of our next meeting.

From the Department of Defense, Jacob Hogue.

JACOB HOGUE: Here.

CYNTHIA POWELL: From Genetic Alliance, Natasha Bonhomme.

NATASHA BONHOMME: Here.

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

SIOBHAN DOLAN: Here.

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

CATE WALSH VOCKLEY: Here.

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

GERARD BERRY: (No audible response.)

CYNTHIA POWELL: I see Dr. Berry.

GERARD BERRY: Oh, sorry, Cynthia, here.

CYNTHIA POWELL: That's okay. Thank you. Okay, anyone who's on who wasn't present when I called the roll?

MICHAEL WARREN: Dr. Powell, this is Michael Warren. I am on.

CYNTHIA POWELL: Okay, thank you, Dr. Warren.

All right. I'm now going to turn things over to our designated federal official, Mia Morrison.

MIA MORRISON: 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 ACHDNC, please let Dr. Powell and I know prior to committing to the interview or presentation.

I also must 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 are also an employee of the organization or unless you have received a waiver from HHS authorizing you to participate.

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

According to FACA, all Committee meetings are open to the public. If the public wishes to participate in the discussions, the procedures for doing so are

published in the Federal Register, and/or are announced at the opening of the meeting.

For this particular meeting, there is no chat feature. However, in the Federal Register notice, we said that there would be a public comment area. Only with the 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 the Committee members are given copies of all written statements submitted by the public. As a reminder, and as stated in the registration website, that all written public comments are part of the official meeting record and are shared with the Committee members.

Any further public participation will be solely at the discretion of the Chair and the DFO. If there are no questions, I'll turn it back over to Dr. Powell.

CYNTHIA POWELL: Thank you, Mia. Can I have the next slide, please? Today I'm pleased to introduce two new Committee members, Dr. Jennifer Kwon and Dr. Chanika Phornphutkul. Dr. Jennifer Kwon is an academic

neurologist with a strong interest in improving long-term clinical outcomes in children diagnosed with rare disorders identified by newborn screening. She trained in pediatric neurology and neuromuscular disorders at Washington University School of Medicine and St. Louis Children's Hospital. She then was on faculty at the University of Rochester Medical Center where she developed an interest in newborn screening and the role of child neurology in the care of infants identified by newborn screening programs.

She is now at the University of Wisconsin, where she is the Director of the Pediatric Neuromuscular Program at the American Family Children's Hospital.

Dr. Chanika Phornphutkul is a Professor of Pediatrics Pathology and Laboratory Medicine at Brown University. She is the chief of the Division of Human Genetics and Director of Genetics and Metabolism Clinic at Rhode Island Hasbro Children's Hospital and is Board certified via the American Board of Medical Genetics and Genomics. Dr. Phornphutkul completed her pediatric residency and pediatric endocrinology fellowship at Hasbro Children's Hospital, Brown University, and did a clinical

biochemical genetics fellowship at the National Human Genome Research Institute.

Dr. Phornphutkul has been a member of the newborn screening task force advising the Rhode Island Department of Health since 2002 and has been the Chair of that Committee since 2021.

Dr. Kwon and Dr. Phornphutkul, welcome, we are very excited to have you on board. Next slide, please.

Within the next few weeks, there will be two Committee announcements posted in the federal register that I want you to be aware of. The first is a call for nominations for voting membership on the Committee. Committee membership requirements are outlined in the Newborn Screening Saves Lives Act. They are that an individual has medical, technical, or scientific experience 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 in ethics, infectious disease and who have worked and published material in newborn screening, and members of the public

having demonstrated expertise or having a lived experience.

To nominate someone else or yourself you must submit the following materials to the ACHDNC at the HRSA.gov website. A statement that includes the name and affiliation of the nominee and a clear statement regarding the basis for nomination, including their areas of expertise in newborn screening. Also, that there's confirmation that the nominee is willing to serve as a member of the Committee, their contact information, and a current CV.

The second announcement in the federal register will be a solicitation for new organizations to send representatives to the Committee. Selections for new organizations will be based on a review of the organization's subject area of expertise, mission, relevancy of their work to newborn screening and benefit provided relative to the Committee's purpose.

Going on to condition nomination updates. In July 2021, HRSA received a nomination package for Krabbe disease also known as globoid cell leukodystrophy. Krabbe disease is both a leukodystrophy and a lysosomal storage

disorder and was first nominated to the Advisory Committee in 2007.

It went through an evidence-based review. However, in 2009 the Committee voted to not recommend the addition to the Recommended Uniform Screen Panel.

The nomination and prioritization workgroup are reviewing the nomination package for Krabbe disease and will keep both the nominators and the rest of the Committee informed of the next steps.

As I mentioned at the November Advisory Committee meeting in October of 2021, the National CMV Foundation submitted a RUSP nomination package for congenital cytomegalovirus. The Nomination and Prioritization Workgroup are currently in the process of reviewing the nomination package for CCMV. I will continue to update the Committee on the status of this package. Next slide, please.

Next, I wanted to talk about updates to the ACHDNC processes. At the November 2021 meeting, the Advisory Committee approved updates to the condition nomination form. For groups that are in the process of developing a condition nomination package, please use the

version of the nomination form on the Committee's website. As a reminder, if you are working on a nomination package and would like technical assistance, both Mia and I are available.

I would also like to highlight that throughout the Committee's review of its nomination evidenced base review and decision-making processes, the Committee received several public comments addressing the potential for the number of condition nominations to outpace the Committee's capacity to review those nominations.

At the August 2021 meeting, the Committee also considered issues concerning this potential situation. I have carefully reviewed the information we have received from the Committee and other newborn screening stakeholders and have identified this as an area of focus for the coming year. Tomorrow, I will facilitate an initial discussion with the Committee to think about ways to approach a potential increase in nominations. Next slide, please.

Thank you, Committee members and organizational representatives for reviewing the 2021 November 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 November 2021 ACHDNC meeting summary?

KYLE BROTHERS: This is Kyle Brothers. I so move.

CYNTHIA POWELL: Thank you. Is there a second?

SHAWN MCCANDLESS: Shawn McCandless, I second. You can have the next one, Scott.

CYNTHIA POWELL: Thank you. Is there any discussion of the motion?

Committee members, when I call your name, please state yes if you are in favor of approving the November meeting summary, no, if you are not in favor of approving the summary, or you may also abstain. And we won't ask our new Committee members to vote on the minutes, I believe, is that correct, Mia?

MIA MORRISON: That's correct, they may abstain from the vote.

CYNTHIA POWELL: All right, thank you. All right, first, Kyle Brothers.

KYLE BROTHERS: Yes.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: Yes.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Approve.

CYNTHIA POWELL: Kellie Kelm.

KELLIE KELM: Approve.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Abstain.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Yes.

CYNTHIA POWELL: Kamila Mistry.

KAMILA MISTRY: (No audible response.)

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Yes.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Abstain.

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

SCOTT SHONE: Approve.

CYNTHIA POWELL: And Michael Warren.

MICHAEL WARREN: Approve.

CYNTHIA POWELL: Thank you. The November 2021 ACHDNC meeting summary has been approved. Thank you, Committee members. May I have the next slide, please. So, for meeting topics of the ACHDNC, we'll meet today and tomorrow, February 11th. Here are the meeting topics for today. First, I will provide an overview of the Committee's new consumer-friendly resources explaining the condition nomination, evidence-based review, and decision-making processes.

Next, we will have the first public comment session of the meeting where we will hear from individuals who registered to provide public comment on the Committee vote on MPS II. Oral comments will be delivered by Dr. Joseph Muenzer, Avram Joseph, Kim Stevens, Dr. Barbara Burton, Amy Cherstrom, Nicholas DiTommaso, Dr. Matthew Ellinwood, and Mark Dant.

Then the evidence-based review group will provide an overview of the evidence-based review from Mucopolysaccharidosis Type II. Afterward, Committee liaisons to the evidence review group, Dr. Jane DeLuca and Dr. Shawn McCandless will present the Committee report on Newborn Screening for MPS II.

At 2:15 the Committee is scheduled to begin the vote on whether or not to recommend MPS II for inclusion on the recommended uniform screening panel. We will end today at 3:00 p.m. Eastern time and reconvene tomorrow morning at 10:00 a.m. Next slide, please.

Tomorrow, February 11th, the Committee will begin with a Phase 2 Evidence-Based Review update on Guanidinoacetate methyltransferase deficiency or GAMT. Then I will facilitate an initial discussion on the ACHDNC Condition Review Capacity. This will be followed by a second public comment period where we will hear from Megan Pesch on the nomination of congenital CMV to the RUSP; Heidi Wallis on the nomination of AMP deficiency to the RUSP; Dylan Simon from EveryLife Foundation for Rare Diseases; Beth Vannoy from Minutes Matter, the MCADD; Mena Scavina from Parent Project Muscular Dystrophy.

Our final session of the meeting will be a presentation on Health Equity in Newborn Screening. We will aim to adjourn the meeting at approximately 1:30 p.m. Eastern time.

I'm now going to turn things back over to Mia.

MIA MORRISON: Thank you. Next slide, please.

Members of the public, audio will come through your computer speakers, so please make sure to have your computer speakers turned on. If you can't access the audio through your computer, you may dial into the meeting using the telephone number and the email with your Zoom link.

As I mentioned previously, this meeting will not have an all-attendee chat feature, but we do have a public comment period scheduled later today. Committee members and organizational representatives, audio will come from your computer speakers, and you will be able to speak using your microphone. If you can't access the audio or microphone through your computer, you may dial into the meeting using the telephone number and the email with your user-specific Zoom link.

Please remember to speak clearly and 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 a comment or ask a question. Simply click on the

participant icon and choose raise hand. I note that depending on your device or operating system, this icon may be in a different location.

To troubleshoot, please consult the webinar instruction page in your briefing book. Next slide, please.

To enable closed captioning, please select the closed captioning icon from your Zoom taskbar in the menu and then select show subtitles from the menu that appears. Thank you.

CYNTHIA POWELL: Thank you, Mia. Can I have the next slide when we can get those up?

EMMA KELLY: I think that was the last slide.

CYNTHIA POWELL: We should have one on the new ACHDNC resources.

EMMA KELLY: Oh yeah, I'll get that up, just one moment.

OVERVIEW OF NEW ACHDNC RESOURCES

CYNTHIA POWELL: Okay, great. For the first session of the meeting, I will renew the new consumer-friendly resources which I'm very pleased to say are now available on the Committee's website. Next slide, please.

By way of reminder, in February 2019 the Committee began a process of reviewing its nomination evidence-based review and decision-making processes. A critical recommendation identified by Committee members, organizational representatives, and other newborn screening stakeholders was the need to develop new consumer-friendly resources explaining Committee processes. These materials were developed in consultation with members of the evidence review group and newborn screening experts, including previous nominators. I would like to especially thank Dr. Alex Kemper and Dr. K.K. Lam, who are instrumental in leading this work. Next slide, please.

The new consumer-friendly resources are all available on the ACHDNC website. Some of the new information is embedded within the current nominate a condition page. There are also six new pages on the ACHDNC website that provide useful information on ACHDNC history and the nomination evidence-based review and decision-making processes.

The new pages are as follows: Condition nomination review process, nominate a condition,

frequently asked questions, key questions considered by the Committee. Sample questions addressed in an evidence-based review. The Committee approach to evaluating the condition review report and the Advisory Committee history page. Next slide, please.

Now I'll briefly go over some of the content on these pages beginning with the nominate a condition page. This was a pre-existing page which has been updated with a new nomination form. On this page, you'll now find both a fillable PDF version and a standard PDF version of the form. From the nominate a condition page you can access all of the new resources as you see circled on the slide, explaining the nomination, evidence-based review, and decision-making processes. Next slide, please.

On the condition nomination review process page, there is an easy-to-follow downloadable graphic depicting the nomination and review process, including when the Committee votes and at what point a condition nomination package might be moved forward or be returned to the nominators. This page includes drop-down text explaining each part of the process. Next slide.

The nominate a condition FAQ page is a valuable resource for groups developing a nomination package or for those who are interested more in learning about how a condition is added to the RUSP. Examples of questions include: how long does the process take to get a condition added to the RUSP? What happens if a nomination is not accepted or is deemed incomplete or not ready for Committee review? What are some tips for developing a nomination package and details on each section of the nomination form? Next slide, please.

The key questions considered by the Committee page provides a concise overview of the information Committee members review in a nomination package. For example, in terms of case definition, are the conditions case definition and spectrum well described? Can they predict the phenotype of the range of symptoms in newborns and children who will be identified through population-based screening? And in terms of clinical utility, is the screening process clinically useful? Is it specific enough to find babies who have the condition, especially those most likely to benefit from treatment? Next slide, please.

The sample questions addressed in an evidence-based review page gives examples and explanations of overarching topic areas addressed in an evidence-based review and the key questions addressed under each topic. For example, for benefits and harms of screening and diagnosis not related to treatment, the website explains that this topic area reviews benefits and harms resulting from newborn screening and early diagnosis. Key questions include exploring the harms of wrongly classifying a baby without the condition as high risk and the harms or benefits of diagnosing newborns found from newborn screening with the condition. Next slide, please.

The last slide I will mention today is the Committee approach to evaluating the condition review report page. This page is based upon the decision matrix guidance approved by the Committee at the November 2021 meeting and provides explanations of using the decision matrix to assign a rating to the nominated condition. Next slide, please.

Members of the public, if you have any questions about these materials, please contact Mia Morrison or myself. I will now take questions or comments from

Committee members followed by organizational representatives. Please remember to use the raise hand feature, unmute yourself and state your name clearly for the record. And I'd also like to thank HRSA for adding all this information to the website and helping with the development of these new resources. All right, any questions or comments about this? Jennifer Kwon.

JENNIFER KWON: So, in Wisconsin we have a similar application process for new disorders and they do take seriously the question of what are -- I think it's easy for advocacy groups and disease families who have suffered from a disease to forget that newborn screening affects a much wider pool. And to somehow dismiss the potential harms of false positives or just the uncertainty that comes with the early screening process, so -- and I just realized as a new member, I already forgot to introduce myself. So, I'm Jennifer Kwon.

So, I just appreciate that that was one of the questions that you put in the harm section. I think that's really helpful, and I think it would be nice to really gather -- you know, I don't know how much work the Committee does in terms of pooling some of these responses

over time from applications that they receive, but I think it's interesting to see what people think of as harms to the greater community.

CYNTHIA POWELL: Yes. I know that there are people out there who are trying to do research in this area, but as you said, it's often very difficult to gather that information. Any other questions or comments? Any questions or comments from organizational representatives?

All right. Thank you, again, everyone who helped with the development of this information. And as I said, you know, if you have any comments or ideas, please contact me or Mia Morrison.

PUBLIC COMMENT

CYNTHIA POWELL: All right, let's see, we'll go to our public comment. As I mentioned in my opening remarks, at the February meeting we will have two public comment periods. Today we'll hear from members of the public that registered to provide oral comments on MPS II. We also received five written versions of the oral testimony that we will hear today and a letter of support for recommending MPS II to the RUSP, which included

hundreds of signatures, and the Committee members received these documents in advance of the meeting.

I think we're ready for our first public comment, Dr. Joseph Muenzer.

JOSEPH MUENZER: Good morning, thank you, Dr. Powell, for the introduction allowing me to speak. I'm a pediatric chemical geneticist. I'm a Professor of Pediatrics and Genetics as a Bryson Distinguished Professor in Pediatric Genetics of the University of North Carolina, Chapel Hill. I am trained as a pediatric biochemical geneticist and have greater than 35 years of experience in the diagnosis, management, and treatment of patients with Mucopolysaccharidosis. In my career I've cared for more than 150 patients with Hunter Syndrome or MPS II.

I strongly support the addition of the MPS II to the RUSP for the following reasons: MPS II is a rare, progressive lysosomal storage disorder due to the deficiency of enzyme iduronate-2-sulfatase resulting in multi-system somatic involvement and a range of clinical severity from cognitive impairment to normal intellect with premature death, unfortunately, in most patients.

Onset of clinical symptoms typically occur between one to two years of age. A diagnosis is delayed until two to four years of age or later in severe patients, and sometimes even later in attenuated patients. Typically, MPS II patients are not diagnosed until after significant clinical disease is present secondary to the rarity to this order and the variable progression of clinical disease.

The biochemical diagnosis is readily available with measurement of urine glycosaminoglycans levels and iduronate-2-sulfatase activity with confirmation by DNA analysis. It is currently available in the form of weekly IV enzyme replacement therapy with iduronate sulfatase that is beneficial in preventing disease progression but does not reverse clinical disease. My clinical experience supports the concept that much of the clinical disease is more irreversible than we initially appreciated. The valvular heart disease is a good example. The progressive storage of glycosaminoglycans in heart valves result in fibrosis which will not respond to ERT and more likely to progress.

It is important to acknowledge that current iduronate sulfatase does not directly impact the brain disease since the enzyme does not cross the blood-brain barrier in any significant amount. However, somatic disease is present in all MPS II patients and IVRT can improve the outcome since both airway and cardiac disease are major cause of death for individuals with MPS II.

A major consideration for adding a disorder to the RUSP is a need to demonstrate that early intervention is beneficial and that waiting to start treatment until a clinical diagnosis is made is detrimental. It's important to note that except for sibling studies, the lack of newborn screening for MPS II makes it very difficult to demonstrate that early intervention is beneficial because of the rarity of the disorder and the significant irreversible disease in patients when diagnosed late. My clinical experience with multiple pairs or preos of MPS II siblings have been that the younger an MPS patient is started on ERT, the better the outcome. The MPS II clinical diagnosis typically only occurs when significant clinical features are present such as coarse facial

features, restricted joint range of motion and noisy breathing.

When treatment is started before the onset of significant disease in a younger MPS II sibling, typically less than one year of age, the outcome is dramatically different with the younger earlier treated sibling appearing like a normal unaffected child, when at the same age that the older sibling was diagnosed with MPS II. Even in the severe and neuropathic phenotype, the younger treated sibling shows better early developmental progress, most likely secondary to improve somatic disease and overall better health.

My clinical experience on the early benefits of treatment for MPS II, also have been dramatically shown by presentations this week at the World Symposium, of lysosomal storage disorder meeting currently being held in San Diego. In earlier result, using brain directed therapies for MPS II, either interfecal gene therapy or IV administered enzyme modified to cross the blood-brain barrier. The youngest treated patients typically less than one to two years of age have consistently the best outcomes.

In summary, newborn screening is needed for MPS II to improve their quality of life and outcomes for the following reasons: One, MPS II is a rare disorder and not typically diagnosed until significant somatic disease occurs between two and four years of age. Two, an improved treatment is available that can prevent somatic disease progression but cannot reverse clinical disease. And three, sibling studies strongly support that early intervention prior to onset of significant clinical disease dramatically improves outcome.

Based on the evidence presented to the Committee and my clinical experiences, I strongly support the addition of MPS II to the RUSP. Thank you for your attention.

CYNTHIA POWELL: Thank you, Dr. Muenzer. We'll next her from Avram Joseph.

AVRAM JOSEPH: Hello. My name is Avram Joseph, Vice-President of the MPS Superhero Foundation. I'm the father of and an advocate for someone who has MPS II. One of nearly 165,000 born boys, one of nearly 400 in the U.S., one of seven diagnoses that were misdiagnosed.

In 2013 my son, Kalal was born. At birth, Kalal was screened for genetic endocrine hemoglobinopathy, immunology and other metabolic conditions. I was told that the criteria for this mandatory newborn screening is that one, it must be a valid screening process. Two, must be deemed a serious condition. Three, must have an FDA approved drug that can be beneficial with early intervention.

Nearly 165 weeks later, in 2016, after constant battles with doctors trying to understand my son's underlying issues, Kalal was diagnosed with a severe form of a genetic metabolic condition called MPS II. This disease is known to steal a child's ability to walk, talk and eat independently by the age of ten. Worst of all, this condition is known to steal the lives of these precious children by the early teenage years. My son was born with MPS II. A condition that with early intervention of enzyme replacement therapy can help give him better quality of life. A drug that is FDA approved and administered on a weekly basis, weekly. Kalal missed nearly 165 infusions of medicine that could have

potentially slowed down the dreadful takeover my son has to experience from MSP II.

Your decision today will define someone else's tomorrow. Although mandatory newborn screening for MPS II is too late for Kalel, it's not too late for the generations to come. Thank you for your time.

CYNTHIA POWELL: Thank you, Mr. Joseph. We'll next hear from Kim Stevens.

EMMA KELLY: There is a slightly problem with her channel now, so she should be able to talk now.

CYNTHIA POWELL: Hi, Ms. Stevens. You can go ahead.

KIM STEVENS: Yes, sorry about that.

CYNTHIA POWELL: It's okay.

KIM STEVENS: Good morning. My name is Kim Stevens and my son, Cole, was diagnosed with MPS II when he was just two-and-a-half. At the time of the diagnosis, he had already had seven surgeries and met with five different specialists. None of them had picked up on his disease.

What I thought was a routine visit to the ear nose and throat doctor for Cole's fourth set of ear tubes,

the doctor took out a very large medical book and pointed to a boy in the book and he uttered those terrible words that no parent wants to hear, I think your son has a rare genetic disease. I was so angry with the doctor that day and even the world. As I look back with nine years of prospective, I realize that was the most important day in Kohl's life. We knew what we were facing, and some quick research showed that there was an enzyme replacement therapy to halt the progression of the disease.

Cole had a very late diagnosis, and a lot of damage had already been done to his body before he could start treatment. But today he is still running around, playing, and eating normally, and I'm grateful for the time the treatment has given Cole with us, our family, and the community. I do wonder what Cole's life would be like if he had been caught at newborn screening. Would he interact and play with his brother? Would must of the progression of the disease be stopped? Would he still have his words and be able to talk to me? The last word he said to me was "Mom." I wish I could hear him say that now.

I'll never know the answers to these questions, but I do know that it was pure serendipity that we saw an ENT that had seen this disease before. Thankfully, he recognized the disease in Cole and Cole got treatment at two-and-a-half. I know others aren't so lucky. They go on a longer diagnosis journey. And my hope for the future is that boys can be diagnosed at birth and then they can immediately seek treatment before the damage starts. We know this damage for the most part is irreversible but imagine treating boys so early that we never see a symptom of the disease. That's when we will truly see a cure.

You have the power to help us today. Thank you for your consideration.

CYNTHIA POWELL: Thank you, Ms. Stevens. We'll next hear from Dr. Barbara Burton.

BARBARA BURTON: Good morning. Thank you, Chairman Powell, and Committee members for giving me the opportunity to address the Committee this morning. I'm a Professor of Pediatrics at Northwestern University and have been a practicing clinical and biochemical geneticist for over 40 years. I would like to express my strong support for the addition of MPS II to the recommended

screening panel. This morning I'd like to focus my comments on the benefits I've observed through pre-symptomatic treatments of patients with MPS II with enzyme replacement therapy.

Since 2006, when ERT became available, I have treated seven sibling pairs in which the older brother was diagnosed clinically with MPS II, leading to the diagnosis in the younger sibling, either at the same time or after a subsequent birth. In every one of these sibling pairs, it was clear after several years of treatment that the burden of disease was significantly less in the younger sibling treated at an earlier age.

In three of these sibling pairs, treatment in the younger sibling was started within the first three months of life. And now at the ages of three, four and ten years, essentially all somatic disease has been prevented. None of these younger siblings have required any of the surgical procedures such as ear tubes, tonsillectomy, adenoidectomy, or spinal cord decompression that have been required in their older brothers. And none have any evidence of cardiac disease or joint restriction. None have coarse facial features. They are essentially

physically indistinguishable from normal, healthy children, although all three of these sibling pairs have the severe organopathic phenotype, all of the younger siblings have shown better developmental progress at each age as compared to their older brothers. Likely the result of improved general health and the reduced burden of disease.

As another example of the benefits of pre-symptomatic treatment, I also had the opportunity to care for two adult men with attenuated MPS II who were cousins and both in their late twenties when ERT became available. While they both received ERT, most of their disease manifestations were irreversible. One already had a tracheotomy and a cardiac pacemaker and died at the age of 40 with respiratory failure. His cousin succumbed to the disease at the age of 36 years from post-operative complications following aortic valve replacement surgery, which was necessitated due to critical aortic stenosis.

A younger cousin of these two men was diagnosed shortly after birth in 2006 because of the family history and started on ERT a few months later when it became commercially available. I've cared for him throughout

this time. He's now 15 years of age and is a healthy, normal appearing young man of normal stature, normal height, normal physical exam. He has no evidence of cardiac disease, has normal pulmonary function studies, normal endurance and to most observers would appear to be a perfectly healthy, normal teenager. He's a great student and he's a high school football player. I have no doubt that his future will be entirely different than that of his other affected family members. I want that outcome for all children with MPS II, and I strongly believe that they all deserve the benefit of early treatment. Thank you.

CYNTHIA POWELL: Thank you, Dr. Burton. We'll next hear from Amy Cherstrom.

AMY CHERSTROM: Hi. Hi everyone. My name is Amy Cherstrom. I'm a mother of two children with MPS II. A little over 11 years ago my husband and I met Dr. Barbara Burton in an exam room in the Children's Memorial Hospital of Chicago. At that time, we were enjoying life as parents of two boys with another due in a few months. We were meeting with Dr. Burton after our son, Alex, had unexplained respiratory distress at birth, radiological

findings, chronic diarrhea, an enlarged head and was due to have an MRI to explain some of the abnormalities.

Alex also had a UPJ obstruction that distracted all of us from the underlying disease needing to be discovered. I resisted as Alex had been through so much and were already so tired of what seemed like problem, after problem, after problem. Our oldest son had been healthy and cruising through his young life without a hitch. Our pediatrician sent us to his colleague, who took measurements of our heads, reviewed all the symptoms, and referred us to Dr. Burton. We knew it wasn't good when he gave us his personal cell phone number and told us not to read anything online about what he thought Alex had, something called mucopolysaccharidoses.

My first question to Dr. Burton was, is there any hope? Everything I read is tragic and devastating. To that, Dr. Burton replied, you have to have hope. You are his mother and MPS II has a treatment. At two years old Alex was lucky that his diagnosis came relatively early, and he saved his brother's life, who was due two months later. Alex began enzyme replacement therapy as soon as his diagnosis was confirmed. At eight months

pregnant, I took an adorable little toddler with big blue eyes and sandy blond hair to the hospital weekly with his favorite fire truck videos and movies to entertain him during an eight-hour day at the hospital.

Along with his diagnosis came weekly treatments, but also surgeries, therapies, educational supports to help Alex address the damage that had been done by this disease in just two short years of his life.

Nick arrived on a snowy day in December, and we were so hopeful. He was a perfect little button with dark brown eyes. He looked like our oldest, Jack, who doesn't have MPS. Is it possible we could be so lucky that he escaped MPS II? There was a 50 percent chance, but everyone was ready in case he, too, would have this disease. He spent about an hour in recovery before going into respiratory distress at full term. This time we knew. Nick was diagnosed almost immediately, and testing confirmed his MPS diagnosis right away. As soon as we leave the NICU, we had that diagnosis.

Nick began enzyme replacement therapy at three months old and we were hopeful. He began to thrive and grow and to be everything we never knew we needed to

encourage us that life would be okay with MPS II. We could live with this disease and even beat it. This was an infusion of hope we so desperately needed.

Nicholas made friends, played baseball and golf, attends our local elementary school, and loves his grandma. He calls her almost daily. While Alex communicates with gestures and an SUD and attends a specialized school for children with autism, each child has one-to-one educational instruction.

As innovation continued, Nick qualified for a clinical trial while Alex took eleven years to find a trial where he would qualify. These trials are life changing with each decision made by us as parents carefully curated to extend and improve these children's' lives. Please consider giving other children a chance through newborn screening to not only survive but thrive. Early access to treatments and therapies makes every difference in disrupting the disease, easing the burden on families, lessening the strain on systems providing services to those whose needs are greater due to illness such as MPS II.

For my family and for those like us who will face a diagnosis of MPS II, please give them the best possible odds of a successful fulfilling life. We're so grateful for the opportunity to tell you or family's story. Thank you for your consideration.

CYNTHIA POWELL: Thank you, Ms. Cherstrom. We will next hear from Nicholas DiTommaso.

NICHOLAS DITOMMASO: Hi. My name is Nicholas DiTommaso. I was diagnosed with MPS II at the age of ten. I'm lucky to have an attenuated version of Hunter Syndrome which has given me the opportunity to be here to speak for all those who don't have the same advantage.

Newborn screening would mean the world not only to those who are diagnosed later on in their childhood but to every patient in the United States. I went through a three-year diagnostic journey before I was diagnosed for something that could have been addressed at my birth. Not everyone who is impacted by MPS II is as fortunate as I have been and irreversible damage from the disease impacts all of us and our families. Even with the attenuated case of Hunter Syndrome the treatment has changed my life in many ways. I felt more energized and many of the

degrading affects that I'd seen rapid onset in my early childhood began to slow or stabilize entirely. Treatment means something different to every patient and their parents and their families, but the impacts of the treatment can't be understated. There are irreversible negative impacts to this disease that take hold for many young people before they display enough symptoms for diagnosis. Newborn screening would help by preventing these degenerative impacts and improve the quality of life for all future patients.

There are many other adults like me who have the opportunity to go out in the world and contribute because of enzyme replacement therapy. It's an invaluable resource that has changed the course of our lives. I was able to attend college and enter the workforce without many severe medical complications. This path to success would not have been possible without the treatment that I started receiving twelve years ago. Because of my treatments I was able to take on an enriching curriculum and find myself with a career in healthcare, which has been an interest my whole life.

We have spent countless hours and resources into producing this life altering treatment and it isn't being used to its full potential. The most valuable time to receive the treatment for me, myself, and many others was years before we did. I am lucky to be able to participate in advocacy that has brought us to this point and the benefits that we can capture are right in front of us. The resources that go into the diagnostic journey for myself and many other MPS II patients could be freed up with access to newborn screening. We've come so far in the past fifteen years when it comes to diagnosing and treating MPS II and now we can put that diagnosis and treatment squarely in the hands of the next generation of patients.

I want you all to take away that I am, but one person impacted by MPS II, and there are hundreds of other individuals out there, not only patients, but mothers, fathers, brothers, and sisters who don't have a chance to be here today. And early diagnosis would not only improve the lives of the children with these conditions, but of all the people who they share their lives with. I have met numerous amazing people with their own MPS II stories,

and I hope that we can realize what a great opportunity we have in front of us. Thank you.

CYNTHIA POWELL: Thank you, Mr. DiTommaso. Our next speaker will be Dr. Matthew Ellinwood.

MATTHEW ELLINWOOD: My name is Dr. Matthew Ellinwood, and I am Chief Scientific Officer at the National MPS Society. I have been active in MPS research and in the society for over two decades. I'm honored to speak to you today as I am honored to be the co-nominator of MPS II for inclusion on the RUSP and to have served on the TEP reviewing this nomination.

Early on in my career I met for the first time a senior scholar well known to the MPS clinical research and patient communities. He had a refrain that he used to open virtually every talk he gave. It was that our mission was to develop technology, to drive the discovery of both an effective therapy and a means of early diagnosis. Through the concerted efforts of industry and the biomedical public health and clinical research communities we have made the needed progress to fully accomplishing these goals.

The most important key now needed to unlock the full benefits to MPS children can only be provided by this Committee today. Indeed, yours is as critical a decision as it will be momentous to future MPS children, and I urge the Committee to accept this nomination and to forward your recommendation to the Secretary of Health and Human Services to add testing for MPS II to the Recommended Uniform Screening Panel.

I could further detail today the sophistication, flexibility, availability, economy and accuracy of our first and second tier testing modalities as well as the benefits of current treatment regimens and those that are on the horizon, including those that have the capacity to fundamentally change the outlook for neuropathic forms of Hunter's Syndrome, such as the two CNS treating therapies proved in Japan and the two currently in clinical trial, or the gene therapies and combined gene therapies and stem cell transplant therapies that are apodized to initiate clinical trials.

However, in addition to my role as the chief advocate for science at the society, I'm equally an advocate for all patients living with MPS and lysosomal

disorders and their families. You have heard from persons with MPS II in their families on the potential impact your decision today will have, but I wanted to spend a moment to detail just how committed our society and its allied communities are to supporting all of the newly diagnosed MPS II infants who will benefit from your approval of this nomination today. The community that has been developed around these diseases over nearly five decades is standing ready to help ensure that patients are well treated and well supported after their diagnosis.

As an example of the size and engagement of our community, I'd like to provide you with a highlight. Among the submitted written comments in support of this nomination, it's a letter the Society wrote. Two-and-a-half days before written comments were due, we solicited co-signers of this statement of support of the nomination. I think we would have been happy with 200 signatures. It became very clear after we had 200 signatures in under an hour of putting out our request, that we were going to garner many more. The total number as I finished my draft of these comments was at approximately 3,050 co-signers. This includes individuals from virtually every state in

the nation and those affected with these diseases, their families and extended families, friends, community members, researchers, industry partners, clinicians and members of the allied health professions all urging you to accept this nomination.

The Society stands ready to put all our resources possible toward the successful roll out of this newborn screening initiative. The Society's experience with pathways, our newly diagnosed outreach program with its dedicated staff member mean that we are ready to provide in person social support and outreach to newly diagnosed families.

In addition, there is an extraordinary community of support, not just from the Society, but from the wider communities of families and from our allied MPS II organizations. All are committed to support newly diagnosed families to ensure they understand all the nuances necessary to optimize the health of their newborn MPS II children.

Finally, as I conclude my comments, I want to put forward a very simple and, I think, accurate proposition. A child born with MPS II deserves to have

this diagnosis at birth. There is simply no reason not to do this. The fundamental basis of therapy for MPS disorders is grounded on prevention of clinical science, not their reversal. Waiting until clinical diagnosis is apparent is waiting too long. Irreversible damage will be done while we wait for clinical science to present themselves.

Approving this nomination is also an issue of equity. We have become mindful in recent years of the disparities of equity in this country around healthcare and access to it. Instituting newborn screening for MPS II ensures that every child born in a state where newborn screening includes MPS II has all of the opportunities to lead as normal and healthy a life as possible.

As I close my remarks, I'd like to express my admiration of all the professionals and dedicated staff who have been part of this submission and its evaluation. They have delved into a great deal of material, data, minutia and produced an excellent review of the evidence available for this rare disorder. But in the last analysis, I urge you to consider your decision today as a matter of whether an MPS II child born in the future will

have all the benefits they deserve and that we can provide. Thank you for your time and thank you for considering my remarks.

CYNTHIA POWELL: Thank you, Dr. Ellinwood. We'll next hear from Mark Dant.

MARK DANT: Good morning. My name is Mark Dant. I'm the Board chair of the Washington DC based EveryLife Foundation for Rare Diseases. I'm also an MPS parent, as my son, Ryan, has MPS I. Ryan was diagnosed in 1991 at the age of three-and-a-half, years before a treatment would be available and long before newborn screen was possible for MPS I. Thanks to the partnership between patients, science, physicians, industry and our government, Ryan is now the longest treated person in the world on MPS I's ERT. His first infusion was exactly 24 years ago this Sunday.

Thank you, also, to this Committee that MPS I was added to the RUSP in 2016, and since that time countless babies have a new opportunity to enjoy a full life because of early diagnosis. The physicians and scientists you just heard from are globally renowned for their expertise in Hunter Syndrome. I have personally

been in conferences around the world with each of them, and when global experts reach out to them for the answers, they are seeking on MPS II, and the opportunities treatment and bring their patients. There are simply no better experts to MPS II than those gathered on this call. Physicians, scientists, and patients around the world rely on their opinions and I urge each of you on the Committee to do the same.

We know Elapses does not cross the blood-brain barrier and therefore, will not treat cognitive decline for those with a severe form of MPS II, but let me remind you, Aldurazyme, the treatment for MPS I, also does not cross the blood-brain barrier, but because of its ability to treat somatic disease, and therefore, greatly improve patient outcomes and quality of life, this Committee rightly approved MPS I to be placed on the RUSP six years ago. I've heard the same discussions regarding not treating the brain that were discussed with MPS I and I am reminded of a friend of mine whose daughter, Stephanie, was recently diagnosed with cancer. Within weeks of being diagnosed, Stephanie began chemo treatments to halt the progression of her disease.

We do not base diagnosis and treatment for pediatric cancers on the cognitive abilities of the afflicted. Why then would we allow babies born with MPS II to continue on a long diagnostic odyssey before being treated, when through newborn screening we can successfully diagnose and treat the baby before damage occurs as in all the examples given here today. Hunter boys make take several years to exhibit signs of their disease. Attenuated Hunter boys, just like children with attenuated MPS I may take even longer to present yet the damage their bodies are enduring throughout those years on the diagnostic odyssey continues and many of those changes will be lifelong and not reversible. Hunter disease progresses from birth.

In 2006, the FDA approved a lifesaving ERT for MPS II that prevents the relentless damage of this disease allow us to bring this therapy to the babies who so desperately need it so they may live the life they deserve.

In closing, this past July, my wife, and I had the opportunity to watch our son, Ryan, get married to a wonderful third grade teacher in Dallas, Texas. That

dream was brought to them and us by the partnerships I mentioned earlier.

The week before Ryan's wedding I received a call from a new mom in Southern California, whose infant son, Luca, had just been diagnosed with MPS I through your gift of newborn screening. She said -- she and I spoke about the importance of relying on Luca's physicians and the miracle of enzyme replacement therapy, but we also spoke about my son, Ryan's journey. Ryan has endured twelve surgeries over his 34 years now. Most to try to repair the damage that occurred in his body over the ten years before he began treatment. Published science now tells us because Luca was diagnosed at birth, the pain Ryan has endured will more than likely not come Luca's way. Luca's mom called me last week. Luca started ERT within weeks of his birth and she describes him today not as a sick baby seeking diagnosis and treatment, but as a happy, healthy little boy.

Please give our Hunter babies the same opportunity newborn screening saves lives. This day, this moment, you can save the lives of the next generation of

MPS II boys. Please vote yes to adding MPS II to the RUSP. And we thank you for your time.

CYNTHIA POWELL: Thank you, Mr. Dant. As we conclude this public comment session, I would like to thank all of our speakers, those of you who shared your personal stories and to our clinicians and researchers, thank you for sharing your expertise with this Committee.

NEWBORN SCREENING FOR MUCOPOLYSACCHARIDOSIS TYPE II (MPS II): A SYSTEMATIC REVIEW OF THE EVIDENCE (PART 1)

We'll now move on. At the 2021 May meeting the Committee voted to move MPS II to a full evidence-based review. We received updates on the evidence-based review at the August and November 2021 meetings. Later this afternoon the Committee is scheduled to vote on whether or not to recommend MPS II for inclusion on the RUSP. However, first the Committee will hear three presentations from members of the external evidence base review group on the evidence-based review for MPS II.

After the ERG presentations, Dr. Jane DeLuca and Dr. Shawn McCandless will give the Committee report on MPS II 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 that is all benefits minus any harms from newborn screening. And then consider the certainty about the evidence.

Next, we'll hear about readiness and feasibility from a public health program perspective. Now I'd like to introduce the members of the ERG who will present to this Committee today, starting with Dr. Alex Kemper, lead of the ERG. Dr. Alex Kemper is the Division Chief of Primary Care Pediatrics at Nationwide Children's Hospital and Professor of Pediatrics at the Ohio State University College of Medicine. 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, Dr. Kemper has also served as Deputy Editor of Pediatrics.

Lisa Prosser is the Marilyn Fisher Blanch Research Professor of Pediatrics and director of the Susan B. Meister Child Health Evaluation and Research Center. 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. Current research topics include newborn screening programs, vaccination programs and methods for valuing family spillover effects of illness.

Jelili Ojodu is the Director of Newborn Screening and Genetics Program at the Association of Public Health Laboratories or APHL. He is also the project director of the newborn screening technical assistance and evaluation programs known as NewSTEPs. 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 science from the University of Maryland College Park.

And we'll first hear from Dr. Kemper.

ALEX KEMPER: Thank you, very much, Dr. Powell. I appreciate this opportunity to report on major findings from our evidence review. I know that members of the Advisory Committee have been given a copy of this report, and our presentation today is just going to highlight key aspects of that report. I will begin by discussing findings from the evidence review, and then Dr. Prosser will be talking about the public health modeling.

I'll come back in just for a minute to talk about issues of cost and then Mr. Ojodu will follow up with findings from the Public Health System Impact Assessment. As we go through, we will periodically stop and give a summary of a key findings which I think will help best with keeping track of everything for the decision-making process. Next slide, please.

This is a list of all the people who are involved in our evidence review group. And I would also like to thank Dr. DeLuca and Dr. McCandless for participating with us as Committee liaisons. They

certainly helped us develop a better report and we're very grateful for their involvement. Next slide, please.

And this is a list of the technical expert panel members. The technical expert panel plays a really vital role in helping us to understand the body of literature that's out there and the nuances of the particular condition. I'll just leave this for a second and you can read a list of names. And I've also marked those members of the technical expert panel who also served as nominators of MPS II to the Advisory Committee. Again, I want to thank members of the technical expert panel. It really helps us to deliver the best possible evidence report that we can. Next slide, please.

So, I want to start by providing an overview of MPS II. As you've heard earlier, it's a lysosomal storage disorder due to dysfunction of a particular enzyme, iduronate-2-sulfatase. And that is caused by mutations in the IDS gene which leads to accumulation of two glycosaminoglycans, GAGs. You'll hear me say this through the report, those two specifics one's dermatan sulfate and heparan sulfate. Next slide, please.

MPS II has a broad range of presentation and disease course. It's typically classified as either severe or attenuated, or another set of terminologies that you hear is neuronopathic versus non-neuronopathic. In general, as I go through the presentation, I'm going to be using the severe attenuated terms because that's the language that we saw in many of the reports that we pulled, and I'll be talking more about what the implications of these different phenotypes are as I go through.

About 60 percent of individuals with MPS II have the severe phenotype. But again, it's really important to understand that there's highly variable phenotypic expression and that's what really leads to this broad spectrum of involvement that I'll be talking about this morning. Next slide, please.

So now I want to transition and talk about what we know about MPS II in terms of its disease course and its epidemiology. Next slide, please.

Much of the information I'm going to be providing about the disease course comes from the Hunter Outcome Study. And so, before I drill into the data, I

just want to make sure that everyone understands where the Hunter Outcome Survey, how it fits into things.

So, it was established in 2005. It's a voluntary registry that now draws information from 29 countries. The Hunter Outcome Study, itself, includes patients who are untreated, who received Idursulfase, which you will hear me talking about in a bit, is the enzyme replacement therapy, or hematopoietic stem cell transplant that excludes patients who have received other enzyme replacement therapies or who are on other -- in other research studies. It does include retrospective data on patients who died prior to the initiation of the entry into the Hunter Outcome Study, and as you look across different studies reporting findings from the Hunter Outcome Study, what you learn is there are different ways of analyzing it in terms of using different subpopulations within the Hunter Outcome Study and using different analytic approaches. And as I talk about the Hunter Outcome Study, I'm going to highlight these important nuances as it plays into interpreting the evidence. Next slide, please.

So, the disease course in general has common clinical important features, some of which you just heard mentioned in the public comment period, including cardiac valve thickening. There could be splenomegaly and hepatomegaly. There could be involvement in the respiratory tract leading to obstructive sleep apnea. That's generally associated with the large tonsils and adenoids. Reduced pulmonary function, skeletal disease with progressive joint stiffness and behavioral problems with cognitive impairment.

The hallmark of the severe form is progressive in significance intellectual disability, and the severe form also tend to have more significant behavioral problems. Next slide, please.

This table lists the presentation of common clinical findings from the Hunter Outcome Survey. This includes the first 263 subjects that were enrolled. About a quarter of them had received enzyme replacement therapy at the time of the enrollment, and the meeting agent enrollment into the Hunter Outcome Survey for these patients was 12.2. So, you can see very common conditions, including otitis media, abdominal hernia, and

nasal obstruction, facial dysmorphism. I talk about the organomegaly, and you can just read down the list. But all the things that are listed on this disease affected more than half the subjects with MPS II. Next slide, please.

A subsequent study of the Hunter Outcome Study, this one including 800 individuals who are treated with enzyme replacement therapy and 95, I should say, untreated there, I apology. The median age of symptom onset was one-and-a-half years, and the median age of diagnosis was 3.2 years. So, you can see this gap between the ages when symptoms first developed and when a diagnosis occurred. Next slide, please.

The information on this slide comes from a different study. It was a study that was done in England, and it involved 110 pediatric patients with a median age of 10 years and following them through to adulthood. The survival rate to 21 years was 52 percent for those treated with ERT at any age versus nine percent of those who are not treated with enzyme replacement therapy. So, you can see this really striking difference in survival based --

survival to adulthood based on treatment with enzyme replacement therapy. Next slide, please.

In terms of the epidemiology, based on clinically diagnosed cases, there was a recent review that reported this fairly wide range of .13 to 2.16 cases per 100,000 children. If you look at the rates in Japan and Taiwan, the range was much narrower, .84 to 1.07 per 100,000 children. And then if you looked in the study and you excluded the outliers and then excluded the East Asian countries, the prevalence reported was .26 to .64 per 100,000 children. So again, there's this very wide range in reported birth -- or reported prevalence. It seems to be a little bit higher in Japan and Taiwan, little bit lower elsewhere. But again, there are many outliers that are reported as well. Next slide, please.

Now let's talk a little bit about the process of diagnosis. Next slide, please.

So, establishing the diagnosis is based on confirming low I2S enzyme activity, and normal enzyme activity in at least one other sulfatase, because there are other conditions that you want to make sure that they're not, confirming at the time elevated urine GAG

levels. And so, the diagnosis is really based on these biochemical tests. The molecular diagnosis could be supportive but it's not necessarily confirmatory. And what I'd like to point out is that there are more than 700 variants of the IDS gene. A study from 2013 -- so again, this is a little bit old -- found that about 60 percent of subjects had a private mutation that wasn't clearly predictive of phenotype. However, if you do have a, you know, significant deletion in major areas, those kinds of things, then you can predict that the infant is more likely to have the severe form. But again, the molecular diagnosis is helpful but it's not necessary.

For some individuals there might be, for example, a borderline low I2S enzyme activity or maybe a modestly elevated urine GAG levels, and for these individuals there could be diagnostic uncertainty. And for those individuals, the current recommendations are that they're followed up every six to twelve months for, you know, some period of time based on the biochemical findings. Typically, according to the experts, this can be up to two years before it's clear whether they truly have MPS 2 or not. Next slide, please.

Screening is based on I2S enzyme activity in dried blood spots. It can be done either through tandem mass spectrometry, MSMS on the slides, or through fluorometry with digital microfluidics. I'm going to be talking in a little bit about which states use which approach. There's also an optional second tier test where you can look at the GAG levels in dried blood spots. And again, I'm going to be talking a little bit about this in a minute as I go through state specific information. Next slide, please.

So first I'd like to highlight the screening that's going on in Illinois. SZ71 positive screens that ultimately led to referral to a sub-specialist clinic. There were nine confirmed to have MPS II, 43 who had biochemical pseudo-deficiency, so it looked like their enzyme activity levels were low but their GAG levels in their urine were normal and they were otherwise healthy.

There were nine who were normal. There were five who were last to follow up and there were five who were still in the follow up process. So those are individuals who have, like I said before, it's kind of the

borderline concerning findings who are still being followed on a regular basis.

One thing that I'd like to highlight from the screening activities in Illinois is that although we weren't able to identify systematic information on additional family members who might have been identified after the diagnosis of MPS II, through newborn screening, there were a few interesting cases that we heard about from one referral center that I'd like to highlight. One is a two-year-old brother that was diagnosed based on a positive newborn screen. There was a maternal great uncle who was diagnosed, and then there was also a maternal grandfather who had pseudo-deficiency. Again, pseudo-deficiency doesn't cause disease, but I do want to point out that in a sort of, you know, evaluation of families that these other cases were identified. Next slide, please.

And now I'd like to highlight the screening that's been going on in Missouri. They used internal microfluidics with fluorometry and a second-tier test with dried blood spots looking at GAG levels. They began their screening in 2018 and there's another report that shows a

longer period of time than this table here, but I do want to focus on this table that, again, is not their entire screening history, but screening from January through December of 2020. This was a time period where the newborn screening program with high reliability could give me all the information on the newborns that were screened during this period of time.

So, in this one-year period there were a little over 68,000 newborns who were screened. There were 11 positive screens that eventually led to sub special point of referral. There is one case of MPS II that was diagnosed, two cases of biochemical pseudo-deficiency, one normal, five still in follow-ups. There was one death before referral. This was an infant who was in the neonatal intensive care unit and again, died before diagnostic evaluation could be completed. And there was one family that declined further testing. Next slide, please.

There is pilot screening that's going on in New York with tandem mass spec. I want to be clear though, this is not a statewide screening. It's in a limited number of selected hospitals and it's just too early to

assess the outcome of those screening activities currently. Next slide, please.

Taiwan has also been screening. They screen with tandem mass spec. The screening there is done with consent, and then the other challenge in terms of interpreting the findings from Taiwan is that there are multiple programs that offer newborn screening within Taiwan. They don't work within well-defined geographic areas and each separately reports outcome. So, the details of this are complicated and really doesn't add to the decision-making process. The reports are in the detail -- the details are in the report and I'm going to be highlighting really the significant findings from Taiwan in a moment. Next slide, please.

So, this is the summary slide of the screening information that we have. You can see the location listed on the left. We have Missouri listed there twice. Once, just focusing on the 2020 data and then the other in the published 2018 and 2021 data. And again, we have Taiwan listed twice because they operate with different programs.

The second column is the time period of the data for each program. The next column is the total number of

newborns that were screened. But what I'd really like to highlight are the last three columns. So, the first of these columns shows the number referred for diagnostic follow-up for 100,000 newborns screened. The next column is the number of MPS II cases that were detected. These were actual diagnoses. And then the final column represents the infants who were in that diagnostic follow-up process, if you remember, coming back every six to twelve months for perhaps up to two years. So the number of infants without diagnosis for 100,000 screened.

So, what you can see, first of all, is that the number of infants who were referred for diagnostic follow-up in Illinois and Missouri ranges from, you know, 13 to 15. I think the 16 number, again, is incorporated into the 2018 to 2021. It's really -- you can think of it as, you know, somewhere between 13 and 15 per 100,000 screened are being referred for diagnostic follow-up. Case detection in the United States, in the two programs in the United States that are routinely screening is 1.5 to 1.6 per 100,000 newborns screened, and as you can see, it's significantly higher in Taiwan where those numbers are 2.9 and 4.1 per 100,000 newborns screened.

And then in the final column you can see the number of infants, as I said, without diagnosis who were still in a follow-up process. I would say that number would probably be between .9 and 2.1. The 7.3 that you see in Missouri is likely artificially inflated because it reflects only one year. And so, if it's followed for up to two years, that would make that number look bigger. So, for the purposes of decision making today, the number is likely somewhere between 0.9 and 2.1 per 100,000 screened. Next slide, please?

So, I want to take a step back and just summarize again what we know about screening. So, Illinois and Missouri have adopted screening, and that they have identified newborns with MPS II. There are some infants who are followed because of diagnostic uncertainty. And the thing that I would like to point out to the Committee is that the case detection rate from screening is higher than the expected clinical detection rate, which I showed you before, remember, it was around .6 or so per 100,000 in the clinically detected cases.

We oftentimes see this with newborn screening, that newborn screening identifies cases that for whatever

reason might not have come to attention or maybe the phenotype of these extra cases is somehow different. But again, we see this commonly with newborn screening. Next slide, please.

Now I'm going to transition and speak specifically about treatment. Next slide, please.

So, I've alluded to enzyme replacement therapy previously in this talk. Enzyme replacement therapy is the standard targeted treatment that's available in the United States. Idursulfase is the name of the enzyme replacement therapy. It was FDA approved in 2006, as you've heard from the public comments earlier, it's a weekly infusion. It's given over several hours. It does not significantly cross the blood-brain barrier. In terms of other adverse effects that have been described with enzyme replacement therapy, as with other enzyme replacement therapies that we've discussed, there can be infusion reactions. These are typically treated by slowing down the rate of infusion. Sometimes it requires pre-medication such as antihistamines or corticosteroids, but from all the reports that we've read about enzyme

replacement therapy, these infusion reactions have not led to discontinuation of enzyme replacement therapy.

The other thing that can happen with enzyme replacement therapy is that individuals can develop antibodies to the enzyme replacement therapy. Again, we've seen this with other enzyme replacement therapies. From the reports that we reviewed, these antibodies do not seem to interfere with the overall effectiveness of therapy, and we didn't identify any reports that describe discontinuation of enzyme replacement therapy because of the development of antibodies. Next slide, please.

So, as we dig into the issue of early treatment with enzyme replacement therapy, I do think that it's important that we, first of all, talk about the FDA drug label. It was last updated in 2018, and I'm just going to read this because it's full of text here, but Elapses is hydrolytic lysosomal glycosaminoglycan specific enzyme indicated for patients with Hunter Syndrome. Elapses has been shown to improve blocking capacity in patients five years and older. In patients 16 months to five years of age, no data are available to demonstrate improvement in disease related symptoms or long-term clinical outcome.

However, treatment with Elapses has reduced spleen volume similar to that of adults and children five years of age and older.

The safety and efficacy of Elapses have not been established in pediatric patients less than 16 months of age. And so, again, the drug label does raise this issue about the lack of establishment of effectiveness for the infants that are similar to those identified through newborn screening. I do remind the Committee that the bar is often high for updating the FDA drug label, and we are, of course, going to go through the evidence that we're able to find of effectiveness of early versus later treatment. Next slide, please.

There are other therapies available MPS II, and I -- in the report we describe what's known about these. For the purposes of this presentation, I'm not going to spend a lot of time on it. Hematopoietic stem cell transplantation, HSCT, is a, you know, potential therapy that is available now. But the issue is, there is lack of clear benefit on the neurologic outcomes and of course, it has risk of mortality. So, in general, stem cell

transplantation is not used now for treating infants with MPS II.

There are a lot of investigational approaches under evaluation. There is intrathecal and intraventricular versions of enzyme replacement therapy. There's modified versions of the enzyme replacement therapy that have been enhanced to help with uptake across the blood-brain barrier. There are treatments that have been approved in other countries but not the United States, including a version of the modified enzyme for intraventricular use and a version of a modified enzyme replacement therapy that has enhanced uptake across the blood-brain barrier. Again, those are not approved for use in the United States, so they're not a key topic of the discussion this morning. Gene therapy is also currently under investigation. Next slide, please.

So, let's talk about early MPS II treatments. Next slide, please.

So, in terms of the timing, as you've already heard today, Idursulfase really targets the somatic aspects of MPS II. There are no cohort studies out there

that directly evaluate early treatment versus treatment after clinical identification. Next slide, please.

And so, as part of our review process, we look at what practiced guidelines might be out there to guide the timing of intervention. And so, I do want to mention the American College of Medical -- the American College of Medical Genetics and Genomics Therapeutics Committee did develop a practice guideline. This is based on a small Delphi panel, ten specialty experts, and there were no public members on this Delphi panel. Next slide, please.

So, this is a direct quote from the practice guideline, and I'm going to go through the first few of these because it's relevant for the conversation. So, all individuals with severe MPS II or predicted to have severe MPS II based on genotype warrant starting enzyme replacement therapy prior to showing signs or symptoms.

Number two, individuals with signs or symptoms with either attenuated or severe MPS II warrant enzyme replacement therapy.

Then the third point is that in their guideline is that individuals with attenuated MPS II who are not showing signs or symptoms of disease do not warrant ERT.

And so, I'm going to stop right there with that number three, and again, through newborn screening, one would expect to identify infants, some of whom are going to have attenuated MPS II and by the nature of newborn screening are not going to show any signs of symptoms of the disease. Next slide, please.

So, I think it's really important to understand the different perspectives and why this recommendation of number three against routinely starting enzyme replacement therapy for individuals with attenuated MPS II who are not showing any signs or symptoms, where that came from. So, if you read the material that was published with the practice guideline in the appendix, the supplementary appendix material, it's clear that some Delphi panel participants did not agree with that recommendation and felt that at a minimum, enzyme replacement therapy should be offered.

The technical expert panel, the TEP experts strongly recommended offering enzyme replacement therapy to all patients with MPS II regardless of predicted phenotype, even in the absence of clinical findings. And again, remember that there can sometimes be challenges

when you diagnose the MPS II in an infant to predict what the phenotype is going to be. But the technical expert panel wanted to highlight, first of all, that the GAG accumulation leads to progressive involvement regardless of what the phenotype is. You have already heard this. And enzyme replacement therapy will not reverse damage caused by GAG accumulation. As you hear a little bit in my discussion, enzyme replacement therapy can be beneficial for some individuals, even after GAG accumulation, things like reducing hepatosplenomegaly, those kinds of things. But the GAG accumulation itself does cause damage and not all that is reversed by enzyme replacement therapy. There's, you know, specific issues brought up, for example, the involvement in cardiac valves and the joints. Again, we'll share with you that information as we talk about cases. But there really was this different -- strong, different perspectives on things and the technical expert panel felt very strongly about at least offering enzyme replacement therapy to all families. And again, if you read the Delphi panel findings, it was clear that there were Delphi panel members who felt that way as well.

So again, summarizing what members of the -- what members of the Delphi panel said and all members of the technical expert panel said is that parents can really make informed choices about when to start treatment. Next slide, please.

So, I want to highlight what we know about treatment following newborn screening. So, first of all, I don't have the complete information on all individuals who were identified in Illinois, but at least in Illinois, of the seven cases that were identified and that were managed in one referral center, five started enzyme replacement therapy and two families have elected close clinical follow-up, and I can't tell you how long they are into that process of close clinical follow-up, but at least most are opting to begin enzyme replacement therapy. In Missouri, of the three with severe -- the three cases of severe MPS II that were identified started on enzyme replacement therapy, one also received a stem cell transplant and died due to transplanted related complications. Next slide, please.

For the next part of the talk, we're going to explore what we learned about early versus later

treatment, and the first bit of information that I'm going to be sharing with you comes from the registry study, the Hunter outcome study. Next slide, please.

So, this study looked at 481 subjects who were in the Hunter Outcome Study. It's stratified by the age at which ERT began, grouping them into less than 18 months, 18 months to five years and then five or more years. It's somewhat difficult to interpret the findings from the study because there's variation in completeness of the data and the length of follow-up. And outcomes in this report are based on the time since enzyme replacement therapy started, not on absolute ages. So, there are -- you know, children might be compared, or subjects might be compared who are a little bit out of sync in terms of age. Next slide, please.

But what I do want to do here is highlight key findings from this study. So, you know, as you would expect, the urine GAG levels decrease similarly for all subjects once they begin enzyme replacement therapy. The left ventricular mass index remains stable. The liver size decreased with faster reduction of hepatomegaly for

those who began enzyme replacement therapy at a younger age.

And then this particular study separated out those individuals without cognitive impairment who were followed for at least eight years with enzyme replacement therapy and completed the six-minute walk test. So, among these individuals, the six-minute walk test increased with a greater increase for those who started earlier. You can see -- I didn't put them in here, but the confidence intervals are really quite wide, but for those who began between birth and 18 months, their six-minute walk test was 507 meters for 18 months, for five years, 494 meters -- 495. And then for those five or more, about 474 meters. So, there is this small difference in the six-minute walk test.

I'm going to be providing more information about the six-minute walk test that I think is a little bit more clear in a minute, but I think that understanding that there's this pattern is helpful when we do get to that information. Next slide, please.

So, as I mentioned before, you know, we don't have the cohort studies or the clinical trials directly

comparing earlier versus later treatment. Again, those would be difficult to do, given the rarity of MPS II. And so, we look to case reports and sibling studies. And I'm going to summarize the key findings from those reports here. Next slide, please.

So, for enzyme replacement therapy in the first year of life, we found the case series of eight infants who were diagnosed based on family history and then treated with enzyme replacement therapy. For follow-up somewhere between -- follow-up with six of them for between 20 months and five-and-a-half years. So again, these -- you know, there's always so much heterogeneity within individual cases and then when you put them together you end up with, you know, these wide ranges of follow-up and incomplete information. But if you just look at these individual cases, for those who began in the first year of life, there did seem to be normal growth, minor joint impairment, improved development, decreased hepatosplenomegaly and there was one subject who had mild aortic valve stenosis with insufficiency. But, again, this kind of case series is hard to interpret because of the lack of standardized measurements at standardized

times and of course, there's no comparative group of individuals who got treated later. Next slide, please.

And so that's where we really look to the sibling studies. You can think of them almost as a matched case study. And in interpreting -- oh, and I should have mentioned before in the Lampe study those were actually all subjects who were in the -- actually, let me go back, because I just want to be clear. You can go back one slide.

These were all infants who got treated before six-and-a-half months of age. So, it really -- really only about halfway into their first year of life. Next slide, please.

All right. So now let's go back to the sibling studies. As I talk about the sibling studies, one of the key points to remember is that siblings with MPS II are expected to have a similar phenotype. And so, it really does provide this natural comparator for early versus later treatment. We stratify things at seven months and actually lines up nicely with the Lampe study that I just described which is why we needed to go back to that. But we -- for under seven months there were three articles and

two conference abstracts that described seven sibling pairs. And then at seven months and older, there was one article, one conference abstract that together described two sibling pairs. Next slide, please.

So, I'm going to go through a series of tables now. Each table reflects one of the particular studies that we talked about. I'm going to start with those who received enzyme replacement under seven months of age, and we've -- even though, you know, these reports oftentimes don't -- you know, they don't follow the order of this table, we really spent a lot of time trying to match things up in a similar sort of way so you could compare across things.

So, you can see in the middle column we describe what was going on with the older sibling whose diagnosis led to early identification in the younger sibling. So, the first one is where the older sibling was two years and seven months, and the younger sibling was less than one month of age. And then for each of them you can see what they're presenting signs were at the time of enzyme replacement therapy initiation and then for follow-up. Again, follow-up is a variable across all these studies,

but what I highlight is that in this case the younger sibling did not develop the coarse facial features that are associated with MPS II did not develop hepatosplenomegaly, did not develop cardiac dysfunction, and had stable joints with less involvement of the skeletal system.

You can also see in the bottom row that there is a marked difference in development quotient between the older and the younger sibling. Next slide, please.

Here is a study where the older sibling was diagnosed at five years of age, the younger sibling at 14 days of age. The older sibling had -- again, is expected a much longer period of follow-up, but again, to highlight, and this is consistent with the other case, there are reported the younger sibling had better outcomes, including not having the joint involvement that his older sibling had. And you can see there is this difference in IQ as reported in this study between the two siblings. I should say, you know, and I should have mentioned this at the start, this report is a little bit harder to interpret because the older sibling is a female. So, this is an excellent condition and so, as would be

expected, there are far fewer females that are identified with MPS II. We can find some cases of older females with it, but again, I just want to highlight that this case is a little bit unusual in that the older sibling is a female. Next slide.

This is another one comparing a diagnosis in a two-year-old leading to identification in the first month of life. You can see the differences in outcome as you look towards the bottom of the table. Again, there was a difference in development quotient between the two siblings. And where you see a blank in the table, it's because the information was not reported in the information that we have from the study. Next slide, please.

So, this is a very recent kind of hot off the press abstract that was accepted to the World Symposium. This one has three older siblings and three younger siblings. The age of diagnosis of the older siblings was between 21 and 36 months, and obviously, the younger siblings were identified quite earlier. You can see that the younger -- the three younger siblings did not have many of the findings that the older sibling had. Again,

the older siblings did have some improvement with enzyme replacement therapy, for example, we talked about the hepatosplenomegaly, but in general, they had much more involvement than the younger siblings that were identified because of the older siblings. Next slide, please.

This is another fairly recent abstract comparing a sibling who was diagnosed close to three years of age and another one at one month of age. Again, you can see the information that we have in terms of follow-up after five years versus 11 years on the older sibling. This younger sibling did have more involvement than was reported in some of the other reports. But again, you can also see from this table that there is information we're missing on this one. Next slide, please.

All right. Now we're going to transition and talk about the older children. So, these are individuals who were diagnosed at seven months or older. This is one that was also recently accepted for presentation comparing an older sibling who began ERT around five years of age versus the younger sibling at 1.7 years of age. Again, we have limited information from -- about this case. Next slide, please.

This table reflects a manuscript that was really hot off the press, just published very timely for us, that compared an older sibling who is three years, eight months of age at the time of diagnosis to a younger sibling who was diagnosed at 12 months of age and began enzyme replacement at 13 years -- or 13 months of age. You can see that this one has a longer period of follow-up in some of the other studies that I shared with you and certainly has much more information. In general, as you can see -- and I should mention that this -- the younger sibling received many other interventions including intrathecal enzyme replacement therapy and has been involved in a trial for the enzyme replacement therapy that crosses the blood-brain barrier. But in any case, you can see that the younger sibling has had much improved outcomes compared to his older sibling.

This individual -- the younger sibling does have significant behavioral involvement, but he is also able to do things like bathe independently, dress and toilet, those kinds of things. I will say that the older sibling, because of the progression in neurologic problems and the lack of continued benefit from enzyme replacement therapy

did leave the family to discontinue targeted therapy for this older sibling, again, because of the severity of symptoms. Again, the younger -- the sibling is having significant behavioral problems, but overall is doing much better in terms of ability to ambulate and dress and those kind of activities of daily life. Next slide, please.

Now I mentioned before the six month -- the six-minute walk test, and I think that it's helpful to compare the two siblings that I just described in terms of the ability to ambulate. So, the older sibling at age 11, and you can see that that's the older sibling is the green on the top, and the younger one on the bottom. The older sibling had limited assisted -- limited ambulation required assistance at 11 years of age. The younger sibling is fully ambulatory at the same chronological age as the older sibling. So, in other words, is doing well in terms of ability to ambulate.

I thought that this was a particularly interesting thing to talk about because if you look at the Hunter Outcome Study, the six-minute walk test findings were less dramatic related to ambulation. Again, you know, we have limited cases, and again, you know, caution

should always be taken when generalizing from one particular sibling study. But I do think that it's interesting to see how much of a difference there is. And again, this particular report, we have such rich information about all the care that the siblings received versus some of the gaps in the Hunter Outcome Study that I talk about where, you know, data are incomplete and stuff like that. So again, I do think that this is an important finding that the Committee should keep in mind. Next slide, please.

So now I'm going to summarize the sibling study. So early treatment was consistently associated with improved somatic outcomes and the ability to perform daily activities. That being said, there's challenges related to heterogeneity in terms of the phenotype, the timing of treatment, the outcome measures that were used. Also, if you especially look at that most recent report, there does seem to be these positive impacts on families associated with earlier treatment. Next slide, please.

So, I'm going to back up and just talk about treatments in general. So idursulfase, again, treats the somatic components of MPS II and is associated with a

decreased risk of mortality by adulthood. It seems to be well tolerated. Again, we didn't find perspective or retrospective cohort studies comparing ERT in the first year of life that later treatment with standardized measures at specific ages. But the sibling case reports that we describe provide indirect evidence of an early treatment benefit, and there are many other targeted therapies that are in active areas of research.

Again, I didn't discuss those this morning because of our focus on the targeted treatment that's available in the United States today. Next slide, please.

So, what I'm going to do now is turn things over to Dr. Prosser, who is going to talk about the projected population level outcomes of MPS II in newborn screening compared with clinical detection. So, Dr. Prosser?

LISA PROSSER: Terrific. Thanks so much, Alex. And so good afternoon, or it is just good afternoon, everyone. Thanks for the opportunity to share these results. So first I just want to take a moment to thank the modeling team here at Michigan, Angela Rose, and Janet Crude who have worked very hard in the last few weeks in

terms of putting these projections together as well as the rest of the evidence group. So next slide, please.

So, the goal of the population level modeling is to compare projected outcomes from MPS II newborn screening for all newborns across the United States and compare that to usual case detection in the absence of screening. Next slide, please.

And so, the approach that will be applied in the modeling analysis here will be evaluating outcomes for an annual U.S. newborn cohort of 3.6 million. We will be comparing screening outcomes. So, screening outcomes, cases of MPS II diagnosed as well as false positives, compared to the number of projected confirmed cases of MPS II in the absence of newborn screening. Next slide, please

In previous condition reviews we have typically also included longer term outcomes. Although longer term in the context of newborn screening is typically still within the childhood period. But in previous condition reviews, we have also included outcomes such as death, cognitive impairment, or the need for mechanical ventilation to provide some additional information on the

health benefits of newborn screening identification and treatment compared to clinical identification and treatment.

But in this situation, there was insufficient data from the MPS II cohort studies to model these in longer term slash short term outcomes after the newborn screening diagnosis and compare that to clinical identification. Because in order to conduct that part of the analysis, it requires standardized outcome measures assessed at comparable ages stratified by age of diagnosis, and Dr. Kemper has highlighted some of the limitations to the studies that were available for MSP II.

And again, although sibling studies are very informative, they're not sufficient to form the modeling. And again, before I move into the details and all, I just want to be very clear here that, you know, this does not mean that there is not evidence of benefit of earlier treatment, but that there was insufficient evidence to quantify the magnitude of the incremental benefit that would potentially be associated with earlier identification, diagnosis and treatment with newborn

screening compared with clinical identification. So, I just wanted to highlight that. Next slide, please.

And so then just before we jump into the model, decision analysis, the methodology that we're using is a systematic approach to decision making under conditions of uncertainty. And the goal here, especially given the level of precision that we typically have with data and evidence around newborn screening, is that the goal is to project ranges and so not to focus as much on any of the point estimates but really to look at the ranges as a representation of the potential short- and long-term outcomes, in this case, just focusing on the short timer outcomes.

Decision analysis or decision modeling also allows decision makers to identify which alternative expected to yield the most health benefit, although here in this case, we're not modeling those longer-term outcomes but still, there's an opportunity to understand the magnitude and the projected range of the different categories of screening outcomes. And decision modeling in general allows for the identification of key parameters and assumptions. Note through the ranges and the level of

uncertainty in the projections. It can be considered in another approach to evidence synthesis, that it reflects the underlying robustness of the evidence-based in general. Next slide, please.

So, I'm going to walk you through the model schematic. So here there are -- what happens in the model is that kind of running across the top of the model that there are identical cohorts of hypothetical newborns. And again, these would be newborns that are not at higher risk. Otherwise at higher risk for MPS II under the assumption that if siblings, you know, are likely to be identified earlier because of the fact of being in that family and there could be other potential risk factors that they were being screened. So again, not otherwise at higher risk.

So going across the top of the model here, so for newborns after newborn screening test that there is some probability of a positive screen, or of a negative screen. Again, all the arrows represent probabilities that we'll go thorough and how those were prioritized on the next slide.

Once there is a positive screening following confirmatory testing, the final categories of outcomes that are being modeled, confirmed positive, and this could be severe or attenuated. These are all combined within the confirmed positive category. Unknown and this is not truly unknown, but this is the category that Dr. Kemper described earlier when describing the laboratory outcomes. So, these represent cases that have diagnostic uncertainty that will lead to continuing follow-up after a positive screening. And this may be for up to one year, up to two years if that's where there is some uncertainty and how long that follow-up period will be. In many cases, it might be much shorter than that. So that unknown is diagnostic uncertainty with additional follow-up following the confirmatory testing.

The next category is false positive. This includes both cases that are identified as normal, following testing as well as cases of biochemical pseudo-deficiency. And then we do include here the category of lost to follow up.

Following along the bottom of row -- of clinical identification, actually, this should be combined into

just one category of MPS II because we're modeling these all together as cases of MPS II model and clinical identification. So, let's move to the next slide, please.

So, this slide represents the definition of the parameters in the model. And so, these are the parameters that populate all of the arrows that were represented on the previous slide. And so just quickly run through this table, but these represent combined data from the Illinois and Missouri newborn screening programs with the most likely, which is a combined estimate and then ranges for each of the parameters in the model. So, probability of a positive screen is 13 per 100,000 with a range of 10.3 to 16.1 per 100,000. And then going through -- I'm actually -- I think it's a little easier to interpret with the rates, but it's parameterized as probabilities in the model, but for MPS II. So, the cases of MPS II diagnosed after a positive screen, that rate, as Dr. Kemper presented earlier, is 1.6 per 100,000 from the combined data and there's a range around that for diagnostic uncertainty leading to follow-up after a positive screen. Similar baseline rate, but a wider range, 0.9 to 5.9, around that.

For false positives, this is projected at 8.7 per 100,000. Again, there's a range and lost to follow up after positive screening of 1.1 per 100,000. The rate for confirmed MPS II under clinical identification, that is being used as 0.67 per 100,000, and this excludes some of the outlier studies, but we have included the full range from reports that have been published from both the U.S. as well as in other countries for the range that are projected. So, if you could move to the following slide, please.

So, this slide shows the projected number of positive screens, looking at the middle column for newborn screening, a base case estimate of 467, that was per year, for U.S. cohort of 3.6 million newborns with a range of about 370 to 580, so a range there.

Then looking at the breakdown following confirmatory testing for MPS II diagnosed. Again, I'm going to focus on the ranges, 42, 59 and comparing that to clinical identification, that consistent with the laboratory estimates that the model would be projecting a higher rate of confirmed MPS II cases diagnosed under newborn screening compared with clinical identification.

For diagnostic uncertainty requiring follow-up, case projected estimate of 57 with a wider range here reflecting the higher uncertainty around this number. And again, there is not a specific follow-up period to find at this point. For false positives, roughly 300 per year, again, with the range around that, and lost to follow-up, and this included the cases that were identified through the laboratory screening that were true lost to follow-up, but also includes one infant that passed away prior to identification. So, let's move on to the next slide, please.

So, in terms of a summary, the projections show that newborn screening would identify a greater number of cases of MPS II compared with clinical identification, that the number of cases requiring follow-up, because of diagnostic uncertainty, but similar to the number of cases of MPS II diagnosed immediately following newborn screening. Again, with a greater range of uncertainty surrounding those estimates. If the cases lost to follow-up, if there had been an opportunity for further evaluation, and also as those cases that are being

followed up resolve, the estimates from this model could change.

And then, just to look back to this -- you know, the decision is really an approach to evidence synthesis that to highlight that this is the first condition considered by the Committee since incorporation decision modeling for which there has been insufficient evidence to model any longer-term outcomes that quantify the potential benefits of screening in terms of specific health outcomes.

And so, I will stop there and hand it back over to you, Alex.

ALEX KEMPER: Great, thank you. And so, what I'm going to do -- next slide, please. Do you want me to do cost now or are you going to do it after lunch?

CYNTHIA POWELL: Why don't we wait and do it after lunch if that's okay with you --

ALEX KEMPER: Okay. That's fine.

BREAK

CYNTHIA POWELL: -- Dr. Kemper. Thank you both. Yeah, so we're scheduled to break until 12:45, so we'll do that and see you back in 30 minutes.

(Whereupon a recess was taken at 12:15 o'clock p.m.)

NEWBORN SCREENING FOR MUCOPOLYSACCHARIDOSIS TYPE II (MPS II): A SYSTEMATIC REVIEW OF THE EVIDENCE (PART 2)

CYNTHIA POWELL: Welcome back everyone. This is the second part of the presentation from the Evidence-Based Review Committee on MPS II. And I think Dr. Kemper was going to be next, is that correct?

ALEX KEMPER: Yes. Yes, you are. You ready?

CYNTHIA POWELL: Yes.

ALEX KEMPER: First of all, I have one small correction to make. I misspoke about the Missouri Newborn Screening a little bit. I inserted -- and this is my fault -- a late change to the term digital microfluidics. They actually use -- they use plate reader fluorometry for the screening separate than the digital microfluidics platform that they use for other screening in Missouri.

And I'd like to thank Dr. Geld for reminding me of this and allowing me to correct the record. All the numbers that I shared, and everything were the same, but I was -- I misspoke about the technology earlier. So now going back to the presentation. As the Committee knows, we are required to look at the newborn screening program cost of MPS II screening. So, this next section isn't the cost of everything related to screening diagnosis and treatment for MPS II but is really limited to answering the question about the cost to the newborn screening program. And as we've discussed previously in terms of our methods given the complexity of the issues and the potential ways that things might change from program to program and over time as well, we really focus on the range of potential costs.

This part of the analysis is led by my friend and colleague, Dr. Scott Grosse, so I am presenting the information, but I just really want to give him credit for helping us think through how to do this. Next slide, please.

So, the cost information I'm going to provide to you is based on interviews with representatives from the Illinois and the Missouri newborn screening programs, and

included were estimated costs related to equipment, reagents, laboratory -- you know, additional laboratory technicians and scientists' time. But again, it's challenging to figure out the precise cost for MPS II screening because it's like every time a condition is incorporated in the screening, it's incorporated into existing activities. Next slide, please.

So, the estimated cost of rough and beyond, the fixed cost of the existing program is between two and six dollars per infant screened. Of course, there again, I had to word digital microfluidics. Just pretend like you don't see that when you're looking at the screen, but the technology, tandem mass spec or fluorometry, the volume of specimens that the program evaluates, the need for additional technician time, commercial assay versus laboratory developed test use, whether or not equipment is rented versus purchased and then there are additional fixed costs, for example, updating the laboratory information management system, the LIMS systems, for example.

It's important to note that because of the low positive first year screening rate, the enzyme activity,

things like second-tier GAG testing or the cost of short-term follow-up really don't substantially impact the cost of screening. Again, the number of infants who require second tier testing or short-term follow-up is small relative to the number of infants who are screened. So again, in summary, the cost is between two and six dollars per infant screened. Next slide, please.

We are now going to transition to the public health system impact assessment, and that will be presented by Mr. Ojodu based on the survey work that's been done. And again, he'll discuss this in detail, but this gets to the readiness and feasibility aspect of the considerations regarding MPS II Newborn Screening.

JELILI OJODU: Thanks, Alex. Good day everyone. My name is Jelili and I'm with the -- can you hear me? Excellent. Next slide, please.

So, before I even begin, I'd like to acknowledge all of the newborn screening programs around the country for not only their work in being essential employees and folks in the Newborn Screening and Public Health System, but for their work in actually completing these surveys for us.

As Alex said, I'm going to just highlight some of the activities related to the public health impact as it relates to MPS II. I'm going to focus some of this talk on the feasibility and readiness of implementing comprehensive population newborn screening and different programs across the country. Next slide, please.

So, this is how we define readiness, and I think we've done this a number of times. I know that there are new folks on the -- you know, Committee members on the Advisory Committee, but we define readiness or a newborn screening program as ready if they can implement a newborn -- a new condition to their old state panel within a year, developmental readiness within one to three years and then unprepared will take a little bit longer than three years to be able to implement. Again, full population mandated newborn screening in their state. Next slide, please.

These are the components of feasibility. Again, these are broad but certainly I want to validate and establish the newborn screening test, the available newborn screening test, a clear diagnostic confirmation approach as well as treatment plan. And then an

established follow-up approach, especially for long term. Next slide, please.

We want to understand, and this is quite important, why. When these conditions are being considered into -- or considered for recommendation to the RUSP, only a few states are screening for it, and so we want to better understand, at least from the other states, as well as the states that are screening, what are the real-world challenges, opportunities, barriers, facilitator? And then to the best of our ability evaluate opportunity cost. Next slide.

So how do we do this? We restart and touched. We developed, among other things, a fact sheet from the states. The two states that you heard quite a bit from about how they're doing population in those states. From their information, we were able to develop and provide a webinar targeted to state programs, develop a survey to focus on each individual newborn screening program. I know it says states here, but there are territories and the District of Columbia that we have to keep in mind as well. Get that information as well as focus on in depth interviews from states that are currently screening as

well as states that are either screening any other conditions on that RUSP, any of the latest conditions, the latest four conditions on the RUSP, all of the conditions that have been recently added to the RUSP and then none of the conditions that have been added to the RUSP to get their understanding of what it's going to take and those barriers and facilitators to be able to implement screening for MPS II. And the last bullet there highlights the additional three states that we focused on. Again, it's the states that are screening for the last four conditions that were added to the RUSP, some that weren't -- that are not screening for all of them, and then some that screen for just some of them. Next slide, please.

So, results, again, I'm not going to say too much about the first two states here. We owe them a debt of gratitude for pretty much everything that they provided and shared with us. The State of North Carolina, we were told, has a IDIQ, what is it, an indefinite -- like it's a contract that was provided to them from an ICHDMIH through RTI in collaboration with the North Carolina newborn screening program to be able to do a pilot -- population

pilot screening for, I think over 140,000 babies born in North Carolina, and that hasn't started yet but I think its anticipated start date is sometime this year.

We heard a little bit about the New York Screen Plus activities. I should qualify that. We heard a little bit from the pilot that is occurring in several or a few hospitals in New York that Alex mentioned in his overview there.

And then the State of West Virginia has a legislative mandate to screen for MPS II but there is no current started anticipated date or a method of screening at the moment. Next slide, please.

So, these are the characteristics of the states that responded to us. And in total, I think -- well, no, I don't think, I know there were 42 newborn screening programs that responded in one way, shape or form. 37 of them specifically to the survey that we sent, and the additional five that were interviewed, includes the two that are currently screening for MPS II right now, and then the three additional states that I have highlighted quite a bit on. This is called the outsource either the newborn screening, whether it's in their state public

health program, regional laboratory, state university or contracted lab or commercial entity. Next slide.

And now we're getting to a little bit of the meat of this -- the survey, and most of this is already part of the report, the comprehensive report that you have as Committee members, but I'm just going to highlight a few things. The question that we ask here in the implementation challenges is, and bear with me, please indicate the following implementation factors for MPS II, and it highlights what are your major challenges, minor challenges, or what would not be a challenge?

And as you can see here, the overwhelming majority of states said that a minor or major challenge was to have the availability of a validated test, increase their fee or address the administrative challenges. And that is a number of things that I may -- I hope I'll be able to highlight just briefly at the end of my presentation.

A number of states, a majority of states did say though that they didn't see any identification of specialists or where they are going to refer folks that may have -- newborns that have MPS II into the medical

home in their state, which I think is something that we -- that we wanted to highlight as a part of this presentation. Next slide, please.

This is a little bit busy and certainly, I'm hoping that the colors show up there, but I'll highlight a few things here. This question was asked of the states that screen, that do newborn screening in their own state, as if they don't outsource the laboratory testing aspect of newborn screening and they do it in their state. The question is the following are considerations or different resources that are needed to provide or implement MPS II in your state. And let us know, you know, when or how long it will take to be able to provide those in your current state as it is right now.

Again, the majority of these states are non-screening for MPS II, so they're just hypothetically given us a sense so how long they think it will take. And as you can see here, the quantity and laboratory equipment to screen for MPS II, which I'll highlight a little bit more about, the sufficiency or the number of MPS staff to be able to notify and track results and LIMS system and adjustment for MPS II where they primary activities that a

number of states said that they weren't able to get within a year. But again, overwhelming majority of folks noted that they are going to be able to and they had full confidence they were going to be able to refer folks or newborns that have MPS II to, again, the medical home, a specialist or treatment centers, that availability in their states. And a few -- let me see here -- let's see, 83 percent of the states said that they were also going to -- they don't have the protocols, follow-up protocols when it comes to MPS II. They can get it within a year, but certainly afterwards, it's possible. Next slide, please.

The question was the following various activities are needed by anyone screening program in order to implement MPS II. Now, implementation, in this case, is for those states that outsource their newborn screening laboratory testing to either another state or commercial entity. And the responses are similar to what we saw earlier for states that are already -- that are going to be bringing on MPS II to their state panels and screening for it and moving forward.

Let's see if there is anything to highlight about this. It's pretty much the same. A good number of

states are saying that they are able to fund and focus -- refer these newborns to the medical home or specialist or treatment centers. LIMS adjustment is something that takes a little bit of time and I'll highlight some of that later. And then the number of staff, again, the sufficient number of staff to be able to report and track results, again, takes a good bit of time, at least a year in moving forward there. Next slide, please.

So, we wanted to get a sense of the barriers and facilitators, both ways, in adding a condition in this case, MPS II in state newborn screening programs. The question is, please indicate the degree to which these factors impede or facilitate your ability to adopt newborn screening programs in your state. As you can see here, the majority of states are focusing on either the non-newborn screening public health priorities, the estimated cost to newborn screening or screening for these conditions, specifically MPS II in this case, and then ongoing activities, and problematic activities, whether it's continuous quality improvement or additional other conditions, again, something that I'll highlight briefly.

Those three were either a minor or a major barrier for state newborn screening programs.

Facilitator, on the other hand, is a number of states note that advocacy in any way, shape, or form, hopefully directed advocacy does actually facilitate implementation, and in this case of MPS II in their newborn screening program.

And there was one other thing that I wanted to highlight as part of this. The expected cost benefit of screening in the state as well. When you added the major and minor facilitator there, it seems like a number of states noted that the expected cost benefit of screening for MPS II is a definite facilitator in newborn screening programs. Next slide, please.

So again, the survey chose, I think, part of what you have already, and so you can go deeper into the questions and the responses from states. But this question focuses on the estimated time it will take your newborn screening program to initiate MPS II in your state. And the majority of folks or states or newborn screening programs, 62 percent said that it would take one

to three years to implement MPS II newborn screening in their newborn screening program.

I would also like to highlight that about 30 percent of those states said that it would take more than 36 months or three years to be able to implement population screening in their program. Next slide, please.

So, I think Alex highlighted this and I want to be able to quickly get through this so that we can get through some of the discussions. Lessons learned from the two states that are currently screening for MPS II, they -- the two states strongly highlighted that there is a good separation between normal and affected for the laboratory test that is currently being used in those two states.

Alex also highlighted this, but the use of a second tier, GAGs, to reduce false positives was certainly something that they wanted us to highlight, and the ability to multiplex with other LSDs is an advantage, or it can be a barrier. It's a barrier or a challenge in some states if you are not screening for LSDs in the first place, and there are a good number of states that are not screening for any of the conditions or LSDs currently, and

so it will still be a barrier to be able to figure out how they are going to be able to bring this on or challenge in a traditional sense.

And then we've highlighted the LIMs or the laboratory information management system revisions and how long that takes in states. Sometimes it can take six to almost 18 months, depending upon the priorities in the states. And then how to handle variants of unknown significance in different states is something that they wanted to highlight as well. Next slide, pleas.

So, these are the lessons learned from the additional three states that we wanted to get the information from, and it certainly helps, at least, for the condition in question, in this case MPS II, to be on the RUSP for them to be able to do a number of things, whether it's increased their fee, rely on other kinds of activities and the readiness tool. These states -- a few of these states actually had a readiness tool and was able to move them from one phase to another quickly, and then a very logical proper way. The three states highlighted, among other things, the different challenges, including funding, hiring of staff, laboratory space and updating

their LIM system as a major barrier to adding a new condition, in this case, MPS II.

And then as noted a few times here, none of the programs actually were concerned about the challenges related to short term or follow-up access or access to treatment in their states. They were fully comfortable, at least as they responded to us, that this -- making sure that the newborns get into a medical home was not going to be a major barrier. Next slide, please.

So, the strengths of the public health system impact, I think we got a really good survey response in almost 80 percent. Again, the webinar fact sheet that we developed from the two states that are currently screening certainly was informational and helpful to be able to know what other states are currently doing. And then certainly, we were able to get a sense of how this particular conditioning, in this case, MPS II, where it's going to be implemented from the other state newborn screening programs. And certainly, the interviews and real-world experiences help quite a bit. Next slide, please.

Limitations, as you can imagine, these are all hypothetical. And again, I'm just going to focus on that last bullet. It's very -- I think that over generalization of what the newborn screening program does, where there are not -- the first two are already being able to do that, is something that we want to be very mindful of, you know. There are 53 newborn screening programs in one way, shape or form, and so there is some variation, certainly, in how those newborn screening programs are able to affect and implement newborn screening programs.

And then the second bullet there and the limited data on screening for MPS II, I think, which has been nicely highlighted by Dr. Kemper. Next slide, please.

Summary. Next slide. A majority of programs said that they will be able to implement or take at least one to three years to implement MPS II as part of their newborn screening population testing. Highlighted the variation of one newborn screening programs and then programs that have either implemented conditions that are already on the RUSP, especially those lysosomal storage disorders seem to be or may be in a better position to be

able to implement MPS II. And I think that is my last slide, but maybe not. One more.

The most commonly reported challenges, and I think this, we need to continue to highlight and emphasize is the ability to increase, among other things, newborn screening and administrative challenges, the staffing issues, whether it's hiring. And then the laboratory capacity for adding a new platform if they are not screening for an LSD or in their newborn screening programs.

And then I would be remised if I didn't highlight the competing priorities in state newborn screening programs and we've all gone through that, certainly over the last year. Next slide.

ALEX KEMPER: Yeah, I think that's the end of the presentation. So, you've now gone through the evidence review, the population health modeling, the public health system impact assessment, and the description of costs. You know, as I was listening to Mr. Ojodu go through his presentation there was one point in the evidence section, which I probably didn't highlight enough, but I did just want to bring up now. It's a small point, but it does

seem that the second-tier dried blood spot GAG testing can really drive down the number of false positives due to pseudo-deficiency. In the main report we referenced some laboratory work that's been done that should have add on dried blood spots, but I know that in the public health system impact assessment part there is a broader discussion of the role of second tier testing that I have in the evidence review part, so I just wanted to sort of close that circle.

Dr. Powell, I'll turn things back over to you.

CYNTHIA POWELL: Thank you. Thanks to all our speakers. We'll now open this up for questions and comments, first from Committee members followed by organizational representatives, and please use the raise hand feature and state your first and last names.

Let's see, I believe we have Cindy Hinton is going to be the ex-officio for the CDC member on the Committee today, and I see she has her hand raised, so I'm going to call on her first.

CINDY HINTON: Thanks, Dr. Powell. Hi, I'm Cindy Hinton, ex-officio member, CDC, and thank you very much to the evidence review group in bringing together all this

information for us to consider. I have a question about the drug label, and Alex, you did point out that on the label it is for pediatric patients five and over. They comment on, you know, no evidence of safety and efficacy for 16 months up to five. And then there's no information underneath 16 months of age.

Have any of -- have the states who have been doing the treatment out of newborn screening experienced any push back from insurance companies or did the Committee learn of any time that an insurance company looked at that and hesitated or, you know, you had to fight to get the treatment? Because when something is added onto the RUSP, it -- you know, insurance companies will the, you know, need to be in line to cover it. So, I just wanted to get some clarification on that issue.

ALEX KEMPER: Yeah, so Dr. Hinton, thank you very much for the question. That is something that we were interested in within the time that we have in our purview, we're not able to systematically assess the degree to which insurance coverage covers the enzyme replacement therapy or individual patient's access to it.

What I can tell you is that I emailed clinical experts in states where they provide therapy as well as another clinician in another state who -- where they dubbed it newborn screening and antidotally they said that insurance access wasn't a problem.

I think that, you know, you speak to two things. One, the FDA label, again, I'm not an expert in what it takes to change the label, but I know that the bar is high in the kinds of sibling studies that we described from what I understand wouldn't be sufficient in and of themselves to modify the label. And then there is also that ACNG practice guideline statement that didn't, at least, promote the use in individuals with asymptomatic -- you know, whatever that is -- MPS II. But the long and the short of it is at least from this, you know, antidotal small sample, it seems like there is access to enzyme replacement therapy.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Thank you. I'm Jennifer Kwon and I had a couple of questions for both Alex and Lisa. Alex, you define this new population of patients who aren't -- they're not false positives, they're not clearly

diagnosed, but they're being followed because of, I assume they -- it's just not clear if they're going to fall into an attenuated or early case, or if they could be false positives. I was just curious, you said that in general the follow-up is for two years. What are they looking for and what are families told about their children's status?

ALEX KEMPER: So, thank you for the question. I can't comment on the conversations that clinicians have with the families, but I -- from what I understand, you know, it's the issue of, you know, slightly abnormal biochemical findings in line to err on the side of caution and just to make sure that there, you know, isn't -- you know, that it's not actually MPS II.

Antidotally, again, I think from what I've heard, at least from one state, they're -- you know, it's probably this way with everything, right, that there's some clinicians who are more apt to want to follow individuals to make sure with great certainty that there's nothing going on. So there probably is some individual clinician variation. But from what we're told it's really a matter of just following them along, maybe every six months or so just to make sure that there's no biochemical

abnormality that would point towards an early presentation of MPS II.

JENNIFER KWON: Okay. And just my second question was for Lisa. You put in your model lost to follow up, and I just can't remember if you've ever done that before for other disorders.

LISA PROSSER: That's a great question, and so I haven't come back and checked, and we've not included that typically before, but in this case, because it was a category that was reported and you know, I won't say to the same significance, but certainly in the same order of magnitude as the other categories about -- again, we're talking about outcomes directly following the screen and confirmatory testing, but if there were cases in there that turned out to be a diagnosed confirmed cases, then given, you know, the various small numbers we're looking at here, that it would change to some extent the results of the modeling. So, we wanted to be clear about reporting those as well.

JENNIFER KWON: Thanks.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Thank you, Dr. Powell. Scott Shone, Committee member. So, I have a question each for Dr. Kemper and Mr. Ojodu, but I first just want to say the cost -- the cost thing just still drives me batty with this putting a dollar amount. The message coming out of this can't be only costing six dollars a screen for MPS II. That might be the cost to run a specific lab test, but the costs are substantially more than that. And again, I just say that and I apologize to be a broken record, but it doesn't take into account all the work that goes before a test is established, the immense follow-up work our team does, the education that has to precede, all the things that go that are never calculated, Scott Grosse and I agree to disagree on how to quantify that, and so be it, but I just felt obligated to say it's not two to six dollars. It's just not. That's not the cost to screen for MPS II, it's the cost to run a lab test perhaps here in North Carolina or anywhere else in the country.

My question for Mr. Ojodu, I guess I also want to say, my fellow laboratorians are eternal optimists, because for the last three or four meetings we've had talk after talk about the challenges we face, hemorrhaging of

people, challenges recruiting, keeping -- we're losing geneticists, we're losing -- we've heard time and time again, but one to three years, boom, magic, all solved. We got this. And I think that we just need to realize that we -- that the survey is the ideal situation and it's been one to three years for every disorder I have ever -- I've been doing newborn screening now for what, since 2000 -- what, 2008. Every survey you guys have done has been one to three years.

So, I just think we all need to realize that's what the survey says but it's going to take us different times because different challenges. So, I appreciate the data but -- so my question for you, Jelili is, did it come up about multiplexing and LDT, because MPS II is not an FDA approved test yet, or FDA clear test yet. And so, multiplexing it is going to cause us to validate as opposed to verify. So, did that come up at all? And then I have a question for Alex.

JELILI OJODU: So, let me just go back to your first comment there, which is that is you're absolutely spot on. Since 2015, there have been four conditions added to the RUSP. 20 states screen for all four

conditions. That represents or that totals about 41 percent of the babies born in the United States.

Your question was on multiplexing. Can you just repeat that again, what --

SCOTT SHONE: Just the challenges with multiplexing because right -- or maybe you know, are there tests coming -- maybe I should ask another question. Is there a test coming that will be FDA cleared that would make multiplexing easier, because it sounds like that's an advantage, but verifying versus validating aren't clinically -- clinical laboratory regulatory challenges, and I just wanted to know if that -- if that detail is flushed out in the assessment of how to add this on?

JELILI OJODU: It wasn't. I've been told that there is the possibility that a test is coming up, an FDA approved test, maybe, but again, this has to come through and a number of things have to happen before that does happen.

I think Alex described this very well. The one state that uses mass spec for newborn screening for MPS II currently screens for other lysosomal storage disorders, and another leukodystrophy plus lysosomal storage

disorders, so they go to multiplex on the traditional way, and certainly, I think when we say multiplex, it's just a little bit different when it comes to -- and again, most states are -- you know, they still don't screen for all the LSD stuff.

ALEX KEMPER: Do you have a --

SCOTT SHONE: I just have an actual question for you, Alex.

ALEX KEMPER: Can I just -- I just want to just follow up on Jalili's response to you before, Mr. Ojodu, I guess I should say for the record. You know, this issue of public health newborn screening program preparedness and readiness is really a very difficult thing to get to and I'd just like to remind the Committee that in order to first do our survey work, we have to have the OMB cleared survey instrument which takes about 18 months to get clearance and the cadence of these reviews are nine months. So, we're kind of stuck a little bit with the kinds of questions that we could do.

But APHL, I think has done some really clever things to be able to get to the heart of what you want in terms of honest appraisal or how long it takes things to

do. So, there's a webinar where states that are doing the screening talk about all the challenges that they've had and what they found works. And then the survey, itself, is completed by teams of individuals from each state that -- and that takes hours for them to do. And so, we're incredibly grateful for the state newborn screening programs that give us their feedback.

We're always open to thinking about other methods to be able to collect this information and to the degree that the Advisory Committee could, you know, come up with the statements, and we really want to know, you know, in reality, how long it's going to take to do things, but it's a very -- it's a very difficult thing to do. And so, if you can think of a better way for us to have the system to do it, we would be like a hundred percent open to that.

SCOTT SHONE: I wasn't criticizing, I just failed to --

ALEX KEMPER: Oh no, no, no, and I don't take it as criticizing, but it's just something that we talk a lot about and I just want to be clear about kind of the restrictions that we have.

Anyone, on to your question which I'm sure now --

SCOTT SHONE: And I'll just say that -- no, but I'll just say that, I mean, Dr. Tanksley is the APHL org rep, but I'm on the APHL Board of Directors and a member of the APHL newborn screening Committee, so I -- so I get it. Like I'm part of that and Jelili hears from me more than he wants to. I just want to share that how the data and the outcomes come out of the survey are critical because they get -- in isolation, they're different from the whole picture, and that's where my comments are, Alex, but let me just -- you had a slides on ACMG, practice guidelines on the Delphi and then your technical expert panel and what is appeared to me to be a disagreement in how to treat kids with different phenotypes, which is always at the heart of the concern of looking at these and how do you parse phenotypes.

And you made a comment, your last bullet on your slide is, parents can make informed choices as to when to start treatment. And I really worry about that statement and I wonder if you can help me understand a little more about that because I worry that parents going to different

clinicians will get different guidance, and as a parent who's had to make treatment decisions for my child, rely on the physician greatly because I've joked on this before, my grandmother will tell you, I'm not a real doctor, right? Dr. McCandless and Dr. Powell and you are the real doctors, right?

So, what I want to better understand is how does that not create an equity issue? It seems to me that depending upon where you can go, you're going to have equity issues if you go to different physicians with different treatment plans. I think SMA and the Cure SMA team and their guidance that came out with the pediatric neurology really nailed it to help us understand moving forward. And the progress we've made with SMA since its addition to the RUSP and identifying babies has really helped with clarity.

Can you help understand, like I don't think it's as simple as parents can make informed decisions.

ALEX KEMPER: Well, you know, so I'm going to go back and focus on sort of the evidence side of things because some of this, of course, is you know, initiative that you all are going to have to weigh in on. What I can

say is that I was surprised when I -- you just moved on my screens, but you're somewhere. Oh, there you are.

So what I can say is, I was surprised when I saw those treatment guidelines, because they really were different than what I've been told by experts, both in states that screen and in states that don't screen, and that's what led me to look at the material in the appendix where they had the comments from each ground of the Delphi panel, and it was very clear that there was a difference in perspective with a large number of people thinking like absolutely, you need to offer enzyme replacement therapy to all children with MPS II, and I don't know, because I wasn't involved with creating these guidelines, if that recommendation three was sort of a passive recommendation that meant sort of like don't automatically start it, or was a -- the way it's written, or a prohibition or a recommendation not to start.

It's hard for me to believe, reading the Delphi panel comments, that there is consensus on that statement three. Now, does that represent disagreements in the field about starting enzyme replacement therapy? That sort of goes beyond, again, what we can do with the

evidence review teamwork -- the evidence review process. I can tell you is that the technical expert panel all thought that at a minimum all families should be offered enzyme replacement therapy.

And then the other thing that's important, I guess a couple things. One is that it's not always possible to predict the phenotype at the time that a newborn is following up after screening, so that creates an issue. And then the other thing that we heard from the technical expert panel, and I think it came through in the sibling studies, is that children who go on to have the attenuated version of MPS II benefit from the somatic, you know, effects, and that individuals who are going to have the more severe or the neuronopathic form, even if it doesn't address the CNS aspects of MPS II benefit. And so, again, I think that there probably, you know, if this moves forward, work that needs to be done with individual states about having consensus about treatment. But from a pure evidence standpoint, you know, that's sort of what we found. I'm giving you kind of a circular answer a little bit because I don't want to weigh in too much with my own personal opinion.

Did I get you anywhere close to something helpful? You're welcome. You're on mute, but I can figure that one out.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: Thank you. So, I actually have question for Dr. Kemper about the pseudo-deficiencies. So, if you look at the first study from Illinois, it looks like that was quite high compared to Missouri. Can you elaborate more the differences between that and those patients -- well, those cases, are they lumped into false positive and are there ways that the newborn screening lab can do to prevent that? I think we encounter this very commonly in MPS I newborn screening and it is a source of, you know, kind of challenges, and I was struck by the differences between two labs, and maybe this is something that we can build on. Thank you.

ALEX KEMPER: Yeah, thank you. Thank you very much for your question and welcome to the Advisory Committee. So, I think that the difference here is the use of dried blood spot GAGs to determine whether or not an individual might have pseudo-deficiency or MPS II. So, I think the difference is in the use of the second tier,

and that's why I brought up those comments before, I really should have emphasized that earlier.

And then getting to your question in terms of the modeling, pseudo-deficiency that leads to referral, if that were to happen, still would be considered to be a false positive. But again, second -- hopefully, you know, and this would correspond everything that we've seen, the second-tier test with -- for GAG would really decrease the number of infants with pseudo-deficiency were ultimately referred to specialty care. You're welcome.

CYNTHIA POWELL: Before we go on, I just want to announce that our Committee member, Kamila Mistry, representing the Agency for Healthcare Research and Quality had some connection problems this morning but is on with us now by phone, at least, and hopefully will let Mia know if she has any questions.

Let's see, Cindy Hinton, did I see your hand up again or --

CINDY HINTON: You did, but my question was addressed.

CYNTHIA POWELL: Okay, great. All right. Let's see, I don't see any other Committee member's hands raised, so how we'll be able to go to Bob Ostrander.

ROBERT OSTRANDER: Yes, hi, I'm Bob Ostrander, American Academy of Family Physicians. Thank you, guys, for a great presentation. I've been involved with this for a long time and I'm just so incredibly impressed at how our discussions and the process has evolved over those years, much easier to follow, much easier to wrap our heads around, I think.

Just as everybody probably knows, but I got into this world because I was part of a medical home movement for children and youth with special healthcare needs, and that kind of is always a lot of the prospective of what I bring, and I'm the follow-up and treatment workgroup. And as I think people know from previous meetings, one of our focuses has been to suggest going forward that the evidence review process look for information, and ideally from submitters of the nomination, a general blueprint of what longitudinal follow-up might look like.

I have a picture of what that might mean for MPS II, but I'm reluctant to assume things for obvious

reasons. You know, Dr. Ojodu mentioned that the labs don't have big concerns about the availability of treatment and getting medical homes set up for these kids, but I'd like to know if that's been looked into a little more than just asking if folks have concerns. As we heard from the oral testimony this morning, these patients, these children, clearly going forward will have a lot of needs, even the ones treated that are addressed by, you know, the traditional form of medical home as outlined in the medical home index going forward, and I don't know if anybody's asked the question of Dr. Kemper, you know, what that picture looks like. It's a narrow enough and rare enough disease, I would think that the specialty care would be at specialty centers and that's pretty well established, although you're going to certainly diagnose more children and diagnose more early. I don't think it would be -- you know, I think it's okay to assume that the capacity will be okay because that may be in rural areas for that. And I wonder if anybody's thought about the two components of longitudinal follow-up, number one, who's going to gather data, not just on disease progression but the other data that we've talked about in the various

papers that our workgroup has published about longitudinal outcome, both medically and with all the other, again, things that are in the medical home index, but also how the interaction between the specialty center and whatever the medical home is, and sometimes that is a medical center, both in terms of medical care for non-condition related things and also more importantly coordination with all the other medical home functions with DME, school, community, rehab and then all that. I really continue to feel strongly that someone should have a vision of that, what the capacity is there and how the education will be transmitted to primary care physicians at the time that these things are added to the RUSP.

ALEX KEMPER: So those are all great questions. I appreciate that very much and of course, as a primary care provider, I -- I -- you know, your question kind of speaks to me as well. I think there were really, if I can unpack your questions a little bit, there's really two different things that were in there. One is the -- you know, the kind of surfaces that an individual identified with MPS II through newborn screening would need, and when I think about this for the evidence review process, it's

really what kind of services does a child with MPS II got diagnosed through newborn screening need versus the kind of services that an individual with MPS II would need if they come through usual clinical detection.

And so, if you look at the sibling studies, I think that's where the most helpful information comes from. So, newborn screening identified cases will likely go on, at least in the United States in 2022 would receive weekly enzyme replacement therapy, and that would, you know, presumably at this point again, go on for the life of that individual. A case that is later detected will also have to receive the same therapy

So, the differences is if you look at the sibling studies, it does seem that there's this like difference in all the other services that individuals might need. So, if there's, you know, if you believe that there are those benefits of early intervention, then the ability to self-care, to ambulate, to not have some of the other long-term sequelae of MPS II are there. So, I think it's really thinking about the difference between, again, the child that was identified through newborn screening versus the child that gets diagnosed later.

There is no doubt that this is an intensive therapy requiring equally infusions, and although, you know, once the child is stabilized and, you know, and the ability to tolerate enzyme replacement therapy is known, home infusions can be done. It's still a really intensive therapy.

The second question that you brought up though is about outcome measures. And I think Dr. Prosser did and especially good job of pointing out the kind of information that we would need to know long term to be able to quantitatively understand the difference between early detection versus clinical case detection. And in the report, and this is the first time we've done this, Dr. Prosser outlined exactly the kind of measures that would be helpful to understand the long-term benefit of early detection versus later detection based on what we know of the disease course and the studies that are out there.

So, does that get to your questions, Dr. Ostrander?

ROBERT OSTRANDER: Yeah, I think it does. I hadn't kind of phrased it in terms of only looking at the

delta between the clinically diagnosed and the newborn screening diagnosed patients, and you know, perhaps the fact that we're already doing what we do with clinical diagnosed patients means that nothing needs to be built into or designed because, again, the early diagnosed patients probably need fewer services. Nevertheless, I'm going to continue to repeat myself at every meeting just like Scott does about his thing, that the more we're explicit about this instead of assuming about it, the better the more advanced medical home system we'll have, and I continue to be overall, not just for this condition, obviously, relatively underwhelmed about how systematic we provide medical home for kids with complicated needs and how much we do it ad hoc, patient by patient and practice by practice, especially in the primary care world. So, I'll get off my soapbox.

ALEX KEMPER: So, noted.

CYNTHIA POWELL: Sabra Anckner.

SABRA ANCKNER: Hi, Sabra Anckner, Organization for AMCHP. So, I just want to thank everybody for their work on this, but most especially the patients and families who shared their stories. I kind of almost, I

think, want to kind of combine some of Dr. Ostrander and Dr. Shone's observations from the public health system's perspective. One is, I know at the last meeting it was requested to have some information about ethnic and racial data for people with pseudo-deficiencies. It doesn't sound like that was available, and I think that that is a problem. That information is out there. We know who those kids are because they had follow-up testing. This -- we have seen, as was mentioned with MSP I, a disproportionate impact on certain populations with pseudo-deficiencies, which means that our tests are inadequate and are not working for those families. We know that false positives in pseudo-deficiencies cause harm and by continuing to note even explore that, it's really, I think, problematic, and goes towards the equity conversations that we're starting to have but aren't really fully really addressing. Like we still want to say well, we screen every baby, and it's like we don't because the test doesn't work the same for every baby.

So, and on that, the cost of programs, as Scott was saying, are so much greater than the cost of what it takes to run the test, especially when there are so many

unknowns, you know, this is sort of an opportunity to combine the worse parts about MPS I and the worse parts of XELD, which is you've got an unknown number of pseudo-deficiencies that are going to occur in populations where we don't know which ones they will be, and you've got an X-link disorder where there's going to be an unknown impact and expectation for following up on extended family members, older siblings, great uncles.

And so that costs time and money and requires expertise within the system. You know, short term follow-up doesn't just call out results, right, they educate providers. They work with their consultants. The consultants, themselves, are overwhelmed. They don't get asked about -- they didn't get asked if they were prepared for this, you know, for patients that they may have to follow for up two years, maybe longer, with indeterminate results, and this -- you know, and I think the challenging part is when we say things like this it is easily framed as not caring about the outcomes for the kids who are affected. And the challenges when you're in the public health system, you are screening every baby, and you have to think about the results and the response for every baby

for every disorder. Most programs continue to not meet the timeliness standards for time critical conditions.

And so, what I want to say with all of these federal funders, on this call with all of our federal agencies on this call is newborn screening programs need money, they need support, they need technical assistance, they need technical assistance when systems of care, as Dr. Ostrander was discussing, with Title V, with CYSHCN Programs, with academic medical centers. These things need to be integrated better. There have been billions and billions of dollars that have gone to the public health labs in the last two years as it should have to build up systems for phrenology, but we need this -- you know, newborn screening is not going away, and the optimism that Scott speaks of is really the pressure to -- we have to save every baby if we can save every baby, but it's not sustainable, it's not possible if things fall through the cracks. And we will continue to see that as we continue to add more and more to the panels without actually providing anymore support, physically through staff and through technical assistance to the programs themselves.

ALEX KEMPER: Great, thank you. I just want to -- and you know, I appreciate the comments that you made, and I do worry about harm. That's something that we think a lot about and it's hard to find the specific elements about that. I just wanted to add in a couple things. One is, I think it's the pseudo-deficiency for MPS II that's probably less of a problem with the second tier GAG testing, but it is those patients with the, you know, kind of slight biochemical abnormalities that are being followed. They're probably, you know, sort of bear more thought. And you can see the magnitude of these issues in the report.

The cost, and again, I just want to go back to the previous questions about cost just so that we're clear on it. So, our charge is to figure out the costs to the lab for implementing the screening. And so, you know, they were based on information that they provided to us regarding the equipment and the reagents and those kinds of things.

The short-term follow-up in terms of adding to the cost is relatively small because it's just, you know, on the order of like a few cases per 100,000. But we

don't -- you're entirely correct that we do not estimate the cost to the clinical systems, and we just don't really have the capacity or the time to do that, which is, you know, part of why it's not in our charge.

The one thing that we did hear from programs though, at least for MPS II follow-up is that they're using the same experts, the same clinical resources that they were using for other similar metabolic conditions, so they're able to follow on those pathways. I don't know if that answers your questions or not, but I just wanted to reflect back on those things.

SABRA ANCKNER: Yeah, I mean, I ran a program, right, so I can tell you that it's more than just the abnormal results, rights? It's -- you know, that's not just -- that's not the only thing that happens in short term follow-up is literally calling out the results. So, it is a bigger burden than that, and, you know, as for the clinicians, I think, again, yeah, it is easy to say like we'll just go to the guys we're already going to, but as we learned in the workgroup meetings last time, the sub-specialists are going no, right? I mean, they're the ones that are saying that, so it's just not reflected in this.

And the other thing that I wanted to say is that with the uncertainty about the clinical guidance on the treatment means your insurance will be deciding for you what your treatment pathways are.

CYNTHIA POWELL: Sean McCandless.

SHAWN MCCANDLESS: Thank you, Shawn McCandless, Committee member. I just want to respond to both what Ms. Anckner and Dr. Ostrander were saying that the reality is that in terms of follow-up, we're taking care of these patients anyways. So, the fact that the numbers look a little different, it reflects the ascertainment bias in the symptomatic, you know, counting symptomatic patients. But the patients, there's not going to be more patients with MPS II as Dr. Ostrander said, if they get on treatment, they're likely to be easier to manage and require less intervention than if they're not being treated. But regardless, we're going to be taking care of them either way. So, I don't want to discount the burdens on the newborn screening lab, but as a clinician who takes care of these patients, it doesn't seem to me that there's -- that this is a big problem. The numbers are small. We're already taking care of these patients anyways, and

frankly, I'll just -- I think I speak for my colleagues when I say we would rather have them healthy and on treatment than when they're -- than coming to us when they're already having multiple surgeries, severely affected and very challenging to take care of.

CYNTHIA POWELL: Debra Freedenberg.

DEBRA FREEDENBERG: I am Debra Freedenberg. I just wanted to speak to comments on costs and system costs, but other folks have already addressed that. There are two things that I'd like to just comment on. One is on the clinical practice. Clinical evolves because of guidelines out there and there's a lot of dissension in terms of whether it's the best path forward. Folks are going to treat them clinically as the way they -- their best judgment is. And so, something that came out in 2018 may not be relevant in 2022 because practice evolves and continues to evolve.

The other question that I had was kind of a theoretical one for Dr. Kemper. The data that's presented in an MPS II, we know that ERT does not cross the blood-brain barrier, however, the data suggests that those that are on ERT treatment either stabilize their cognitive

decline or don't have it if treated early. And I was wondering if there was any point about the mechanism about which to decrease (unintelligible).

ALEX KEMPER: Yeah, so that's a great question. What I can tell you is that it does seem that at least some of the enzyme does cross -- that's why I use the term, significantly cross, but the amount is not great that crosses. I'll tell you that on the evidence review side of things, I try not to -- I try not to figure out like the pathophysiology of why something might make a difference, but what I can tell you from talking to families is that having, you know, a child that can better ambulate and take care of things like toileting and those kinds of things, even if it's not dramatically affecting the CNS involvement, will just naturally lead to differences in, you know, some cognitive skills, those kinds of things. That's not a very scientific answer, but that's sort of how I interpret it.

DEBRA FREEDENBERG: And then my last question is just a comment you just made, and that it's the -- they're looking at the cost estimate for the lab. Is it the lab

or is it the newborn screening program for the cost estimate?

ALEX KEMPER: Yeah, I -- really, it's -- and we talk so much about the cost. I don't know if there's a way to bring Dr. Grosse into the conversation because he might be able to add some additional color commentary beyond what I'm going to say, but it's the cost of the lab, the LIM system, you know, the issues, the short-term follow-up, those kinds of -- you know, like the whole package. So not just the actual test itself, but again, there are so few infants that end up getting referred from newborn screening that it just doesn't appreciably change the range of costs.

And now, ladies and gentlemen, we have a real health economist and I'm going to have him add some additional comments.

SCOTT GROSSE: Thank you, Alex. The conversations we had with the two screening programs in Illinois and Missouri, but that they did not experience any need for additional follow-up staff to engage in these activities. All of our estimates are based from those two

programs. That does not mean that programs in other states might not experience additional costs.

CYNTHIA POWELL: Next, we'll hear from Melissa Parisi, who hasn't had a chance to comment or ask a question yet.

MELISSA PARISI: Thank you very much. This is Melissa Parisi from NIH and NICHD, and I just want to thank you all for your really thoughtful presentations and I've enjoyed hearing some of the details as you've presented them and recognize that with these rare conditions, you know, the data that you have are the data that you have and sometimes there are limitations in being able to extrapolate.

I also wanted to share with everybody just an announcement in case folks were not aware, that our institute, the Child Health Institute, NICHD, is actually supporting a pilot project to screen for MPS II in North Carolina and that's a contract to RTI with the goal of actually starting screening probably around April. The team is currently in preparation, creating all the systems and procedures, IRB approvals, et cetera, and working closely with the North Carolina State Laboratory of Public

Health to accomplish screening for MPS II in North Carolina. So that will also add to the data on the condition. The goal is for them to screen 140,000 babies over the next two years. Thank you.

CYNTHIA POWELL: Thank you. Jennifer Kwon.

JENNIFER KWON: Thanks for letting me speak again. I just -- I think it does bother me a little bit thinking about the patients who are lost to follow up, because I think it gets back to the issue of equity. I think that it is a burden on families who are diagnosed with this disease. It really sounds like a very -- I mean, I think that for the families that have lived through it and who are making the sacrifices to have their children treated, it seems like it's well worth the effort. But I think that we have to remember that in a population-based program, we are going to see a wider range of people and responses, and you know, social factors than maybe we're seeing in families who have, you know, two siblings with MPS II.

And so, I just wonder -- that was the basis for my questions about what's involved with, you know, follow-

up of ambiguous results and why did five people get lost to follow-up, what was going on with that?

The other thing that I'll say is that it would be really a great time for the MPS II community to tighten up their guidelines for treatment, because as someone who routinely prescribes medications, two medications which are on the top ten most expensive medication list, I notice that your enzyme replacement therapy is also on that list, and I will tell you that insurers do care what the FDA approves, and they do care about expert guidelines.

And I think that the final thing that I would point out is the New Steps Program, the website is just terrific, and I take a look at it a lot, and I have noticed that MPS I and Dr. McCandless pointed out that it's going to be the same set of players, really, who are taking care of patients with MPS II, but many states -- I think I counted like 20 or so states have not approved MPS I for newborn screening, and I think it's interesting that there's a similar lag in states for some of the disorders like X-linked DLD and Pompe disease, whereas if you look at the map for SMA, the uptake by states has been very

different, even though the treatments are quite expensive, and I think that we have to think about what happens in that short term follow-up visit when we give people results and tell them what the next steps are. There are families who may find it very difficult to understand that the next step is another visit for more testing to be told again that there's another step, and then you do it all over again. Whereas, what I would say would be SMA follow-up, is that it is a much simpler conversation. I mean, it's a lengthy, complicated conversation and it takes hours, and this is SMA. But it is relatively simple compared to what the metabolic geneticists have to go through when they're counseling patients about MPS II, especially if they're in a state without second tier testing.

And I think that no matter what the labs say and what to do, that must play a role in the uptake of these disorders in state newborn screening programs as well. So, I would encourage you to look at those maps and ask yourself, are the states kind of voting with their feet, and what are the pieces that we're missing when states, despite it being years after, you know, Pompe was approved

or X-ALD was approved, why are so many states still not adding it to their list of diseases that they screen?

ALEX KEMPER: I really appreciate the points that you've made, and I think this issue of like lost to follow-up is such an important area for study, but of course, you know, we don't have that information. But I would love to know, you know, what the factors are that lead to it.

And then the other thing -- I didn't bring this up before -- but I was thinking about, you know, because this is all relatively recent, how much things like the pandemic played into that as well. So, you know, there are so many different things that could be leading to -- and I completely agree about the points you made in terms of, you know, they need to ensure a follow-up, and if people aren't following up, why is that and the risk for health disparities related to those things. These are all like areas that are really, I think, ripe for study.

CYNTHIA POWELL: Thank you. Before we move on to our next session, I'd just like to once again thank Dr. Kemper, Dr. Prosser, Mr. Ojodu for your presentations and

very thoughtful discussions and to all of the members of the evidence review group and experts for their input.

COMMITTEE REPORT: NEWBORN SCREENING FOR MPS II

CYNTHIA POWELL: And with that, I'd like to go to, I think we have a few slides on the matrix. So, for each condition voted the 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 the evidence review, forming a recommendation for the condition rating and overall Committee recommendation and assisting the Chair in leading Committee discussion.

Before I turn it over to Dr. Jane DeLuca and Dr. Shawn McCandless, I want to give a very brief overview of the decision matrix. I know many of you have seen this many times before. We do have two new members of our Committee, and although they heard about it during their orientation session, we also have some members of the Committee who have not been serving for that long where this is really the first condition that we've considered.

So, I'd just like to go over, if we look at under the orange box, net benefit, and certainty, to think about the significant benefit decision and the certainty of that. So, the A1 rating or the A rating means that there is high certainty that screening would have a significant benefit. And if we think about the net benefit, that would be the total of all the benefits minus any risks that we see.

And there is the B rating, which is that there is moderate certainty that screening would have a significant benefit. There is also the public health readiness and feasibility that would be ready -- that most public health departments are ready to start screening, that they have developmental readiness but would generally take one to three years to begin screening, or that they are unprepared for screening. And then whether or not there is feasibility to perform or implement population screening.

So, 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 process is used to guide 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. May I have the next slide, please.

The Advisory Committee adheres to the following principles in developing recommendations: Recommendations are evidence-based. There must be scientific evidence that screening leads to improved outcomes and that these benefits outweigh the harms of screening, that outcomes that matter most are the health benefits to the individual being screened.

The overarching goal of screening is to improve the health-related quality of life of newborns. 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.

Feasibility assesses the resource needs for effective comprehensive screening, including a general

estimate of cost to adopt screening for the condition under consideration. Next slide, please.

Using this part of the matrix the Advisory Committee assigns one code to rate the evidence. A, there is high certainty that adoption of screening for the targeted condition would lead to a significant and substantial net benefit. B, there is moderate certainty that adoption of screening for the targeted condition would lead to a significant and 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. D, there is high or moderate certainty that adoption of screening for the targeted condition would lead to a negative net benefit. And L, there is low certainty regarding the net benefit from screening. Next slide, please.

Once each of the readiness and feasibility ratings are assigned, the Advisory Committee uses the following public health capacity matrix dimensions to assign readiness and feasibility ratings of public health department newborn screening programs.

Number one is that most state public health departments are ready to begin comprehensive screening and screening has high to moderate feasibility. Two, is that most public health departments have developmental readiness and screening, has high to moderate feasibility. Three, is that most state public health departments are unprepared to begin comprehensive screening and screening has high to moderate feasibility. And four, implementation of screening for the targeted condition has low feasibility. Next slide.

Are there any questions regarding the matrix? Okay. Before introducing Dr. DeLuca and Dr. McCandless, I will 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 Genetics Center in the Metabolic Clinic caring for newborn screening patients and others with inborn 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 of Colorado. He is a past president of the Society for Inherited Metabolic Disorders. He served on the Ohio Department of Health Newborn Screening Advisory Counsel for 12 years prior to moving to Colorado. His research has focused on inborn errors of metabolism and Prader-Willi syndrome. He is a fellow of the American College of Medical Genetics and Genomics and is active in SIMD, the Society for Inherited Metabolic Disorders, and the American Society for Human Genetics. And first we'll hear from Dr. DeLuca.

JANE DELUCA: Thank you, Dr. Powell. First, we'd like to thank the evidence-based review group, Dr. Kemper, and Dr. Lamb for their incredibly detailed work in reviewing and presenting evidence for the disorder MPS II.

So, we're tasked as liaison to the evidence-based group as Committee members. So, we do get to see the evidence as it evolves over the course of evaluating a

particular disorder. I would also like to thank the HRSA team for all their support and also to thank Dr. McCandless for his guidance and wisdom in furthering my understanding of research and evidence of MPS II. Next slide, please.

So, Dr. Powell gave us a nice overview of the decision matrix and I just wanted to talk about how our presentation is going to sort of roll out this afternoon. We're going to talk a little bit about and review some of the information that we've already discussed that was presented by the evidence-based group in terms of the disorder, itself. And then we're going to get to some of the core issues in terms of understanding this level of certainty for net benefits as newborn screening for the identification of children affected by MPS II. So, our emphasis is going to be in that area. We will also touch on feasibility and state's readiness later on in the presentation. Next slide, please.

We've just seen this in terms of the matrix. So, we can move on to the next slide, please. So Mucopolysaccharidosis type II is an X-linked lysosomal storage disorder. It affects primarily males with

occasional development -- occasional identification of symptomatic females. Variants of the IDS gene lead to the dysfunction of the enzyme iduronate-2-sulfatase with the accumulation of glycosaminoglycans, specifically dermatan sulfate and heparan sulfate in organs. Glycosaminoglycans, or GAGs are long polysaccharides that are essential in many processes in the body such as cell adhesion, tissue repair and immune response and other actions. When there's an impairment of the enzyme, the GAGs become accumulated within cells and organs.

The prevalence in Japan and Taiwan for the disorder, if we put it at 0.84 to 1.07 per 100,000 births, and in the U.S., it's estimated to 0.26 per 100,000 births. And the difference in prevalence is probably due to reporting and ascertainment methods for the clinical identification of the disease.

Now, in our newborn screening programs that are offering screening at this point for Missouri and Illinois, it's about 1.2 to 1.6 per 100,000 births. Next slide, please.

MPS II is screened by enzyme analysis. There are two methods reported for the detection of the

disorder, the fluorometric method and tandem mass spec. As it had been noted, second tier examination of dried blood spot GAGs can reduce the call outs for pseudo-deficiency.

In confirming diagnosis, repeat enzyme assay is necessary and there's measurement of another sulfatase to rule out multiple sulfatase deficiency. In terms of molecular analysis hemizygous pathogenic variants or deletion in IDS gene can be identified, but this tends to be less useful in predicting a clinical course.

Biochemical profile of urinary GAGs in detection can also help in terms of identifying the condition and family history is important as well as carrier detection through siblings or affected individuals. Next slide, please.

Classification for cases of MPS II can be severe or attenuated. Severe is early childhood onset with neurological deterioration. And attenuated cases have a later onset and somewhat slower progression, but all patients appear to have some degree of neurological involvement. However, adults could have normal cognition.

Symptom offset can occur by 2.7 years for severe phenotype and 4.3 years for attenuated phenotype. As we know, the symptoms can include hearing loss, progressive change in appearance and large liver and spleen, joint stiffness, mobility issues, abdominal hernia and large tongue, tonsils and adenoids, cardiac valve disease, developmental and fine motor issues, and behavioral concerns. Presentation of progression of symptoms can be variable. Next slide, please.

For treatment, there is symptomatic treatment of different presentations and problems that occur with the disorder and appropriate therapies, including surgeries, but one of the mainstays is the weekly enzyme replacement therapy, Elapses, which was approved by the FDA in 2006. This consists of an ID infusion over several hours. Many patients will develop antibodies, and many have reactions that are manageable. It's a rare case where the reactions are so severe that infusions need to be discontinued.

Investigational therapies can include hematopoietic stem cell transplantation, central nervous system delivery of ERT. Investigational ERT has been proposed to penetrate the CSS, which is another treatment.

Insufficient evidence, however, is available regarding the potential benefit of gene therapy. We have the published ACMG guidelines from 2020. Next slide, please.

ERT therapy appears to be associated with a moderate delay in mortality and reduced rates of deterioration in mobility, respiratory status, and cardiac status. Central nervous system disease is not directly impacted by existing therapies, but somatic improvements may allow for better acquisition of developmental milestones.

There's limited evidence supporting benefit of early versus symptomatic treatment. Sibling pairs suggest benefit in terms of early intervention, however, complications in terms of intervention occurs because you can have a delayed clinical diagnosis. The peer reviewed evidence is limited. Much of the assessment of value relies on expert opinion and this is primarily the result of an ultra-rare nature of the condition.

At this point I will hand off to Dr. McCandless, and next slide.

SHAWN MCCANDLESS: Thank you. And I'd also like to echo my appreciation for the evidence review Committee

and for my colleagues on the Committee here today, and particularly for the wisdom of Dr. Powell and Dr. DeLuca as well as our HRSA partners.

You've seen the data on the screen before. These are from Dr. Prosser's presentation. And I just want to highlight a couple of things. The first is that the -- I think you've seen the numbers, you've recognized and heard Dr. Prosser say that it's more important to look at the ranges than it is to look at the actual numbers. But I just wanted to point out that the newborn screening appears to -- we should expect that we will have a similar number of patients that end up with diagnostic uncertainty requiring some period of follow-up and ongoing testing, to be similar in number to the patients that are true positives and identify, and that those patients that are true positives and identified, and that those patients lost to follow up are also not going to -- are also quite significant, as was referred to earlier.

The false positives are mostly pseudo-deficiency and that is generally fairly straightforward to sort out. And so as has been reported in the newborn screening literature in the past, false positives that can be easily

recognized during the confirmatory testing period are probably of less concern in terms of harm from the screening program.

I do want to point out one other thing though. That this diagnostic uncertainty group, in essence, what that's doing is that newborn screening is shifting the diagnostic odyssey from those patients that actually have the condition to those patients that almost most likely do not have the condition but will be given a potential -- will be told that they are at increased risk for diagnosis that will require follow-up for what could be as much as two years. May I have the next slide, please?

The benefit to affected individuals seems to be relatively evident from what we've heard today. There's somatic improvement, slower progression of somatic problems, possibly slower neurologic degeneration which may have -- which may be related to increased acquisition of milestones or perhaps somehow related to the improved somatic benefits. There does appear to be both improvement and stabilization of cardiac symptoms. Respiratory outcomes were improved, at least at age 16, in the study from the U.K.

And then overall survival is really challenging to get at because both of the studies that we saw that addressed this, the Hunter Outcome Survey as well as the U.K. data commingled severe phenotype with the attenuated phenotype when referring to the impact on survival of enzyme replacement therapy to the point where it becomes impossible to actually measure how much of the improvement related to children that were treated with enzyme replacement therapy is due to the enzyme and how much is just due to the proportion of individuals in each group that have a severe or an attenuated phenotype.

With all of that said, there is some evidence to suggest that this difference was found in the U.K. study, and it seemed that their data set was a little bit more clear, and that there is evidence to suggest that this difference is likely to increase with earlier treatment, although that has not been definitively shown or even solidly shown. May I have the next slide, please?

We feel that some reasonable assertions can be made based on these challenging data. The first is that ERT is likely associated with modestly prolonged life. ERT is likely associated with better somatic function.

That may even be more than likely. I think that's pretty clear. And we assume that ERT is associated with improved quality of life. ERT, itself, does not alter the CNS outcome as best we can tell, although it has been suggested that there may be slowing of the rate of neurologic deterioration in patients who are treated, particularly with early treatment.

And it appears that it is reasonable to assert that earlier initiation of ERT likely maximizes the benefit of therapy, although the data are really lacking regarding pre-symptomatic therapy in comparison to symptomatic treatment. May I have the next slide, please?

It's important for us, when considering the net benefit, to consider more than just the benefit to the individuals who are affected, but also to consider the potential harms. And most of the potential harms accrue to individuals that are not affected. And that may be the people with molecular variants of unknown significance, and in particular those with indeterminate results. And I think it's really important to point out that urinary -- quantitative urinary glycosaminoglycan analysis, GAG analysis, is not a dichotomous result. It is a continuous

variable and that there are -- there's a clear normal range, there's a clear abnormal range and those ranges don't meet each other. So, there's what some people refer to as a gray zone in the results where you can't say this is completely normal, but it's not typical for a person who's clearly affected either. And we think that some, if not most of the indeterminate results will end up being due to one of these two categories.

Those of us to follow up, we should be really careful to not ignore what the potential impact on those families and those children is. Pseudo-deficiency results, as Dr. Kemper pointed out, using dried blood spots as a second -- dried blood spot GAG analysis as a second-tier screen appears, from the Missouri data, to reduce the false positive -- to reduce the false positives by about two-thirds from the -- at least from the call outs, from the newborn screening lab. But it's not a hundred percent, it does not rule out a hundred percent of the pseudo-deficiency patients. But those patients are based on other newborn screening literature. People that can be clearly defined early in the course of the diagnostic work up, generally there are not measurable

long-term harms related to newborn screening in other conditions. We don't have data regarding MPS II or MPS I for that matter.

False negatives are a potential harm, but there have been none reported. So, the test itself, the screening test seems very, very good so far. We think it's important, though, to point out that the potential for psychological and financial burdens for families after a false positive screen particularly for those with indeterminate results really have not been explored or defined. And so, you know, we can guess what some of them might be, unrecovered income because of traveling to appointments, lost time, lost quality of life, anxiety and stress for the parents and the cost of monitoring. There may be others. May I have the next slide, please?

So as the Committee considers the net benefit, we are thinking about the balance of the benefit versus the balance of the harms to the population who are undergoing this compulsory newborn screening program. May I have the next slide, please?

And I think it's really important to point out here that the benefits and the harms almost certainly

accrue to different individuals in the population, that the people who benefit are different from the people who are harmed by newborn screening. And as a Committee we have to consider both of those when we're considering recommending a population based compulsory newborn screening program. And I think the question has come up before from several others that we need to be really thoughtful about whether there are reasons to think that different groups may be affected differently by the benefits or harms, the sense of justice and equity. May I have the next slide, please.

So, to kind of summarize this, we're being asked the question, is there significant net benefit for compulsory population based newborn screening for MPS II. And we believe that the evidence is challenging to interpret, largely due to the rarity of the disorder. But it also clearly points to the need for authors of future case reports and case series to be really thoughtful about presenting their data in ways that will facilitate comparison. And this is a message for people who -- for groups who are considering proposing or nominating a condition in the future. The time is now to start

thinking about the data that is required to support your argument.

That said, the bulk of evidence that we've heard today, and the clearly stated experience of the expert clinicians and families shows that the somatic benefits of treatment are very meaningful to families and patients. I use the word, moderate, here in this slide to indicate while the somatic benefits are evident, the potential benefits on CNS involvement and mortality are less apparent, at least in the data available, and in fact, appear to be relatively modest.

I think potential harms we've discussed primarily accruing to those individuals with indeterminate status in our opinion, we do note that the risk of treating patients that was addressed earlier exceeds extremely low. There's an extremely low risk that we will treat patients that will not benefit from treatment, whether they're truly affected or whether they are not affected with the disorder.

We should just also point out here that the cost of screening appears to be relatively high per true positive case relative to other conditions that have been

added to newborn screening in recent years, and this is a combination of the rarity of disease and the cost of the testing itself.

The result of all of this, though, is that -- well, I also -- I would like to go back to the third point here, potential harm. And just say that as we've seen from other nominated conditions, advocates for screening feel very strongly that the benefits that accrue to affected individuals far outweigh any potential harm of the compulsory population based newborn screening program to unaffected individuals and their families. However, we note that no one speaks here for those families that may be experiencing harms. That's understandable. It almost certainly reflects the imperfection in the process which by the way, has gotten better and better over the years. But the fact that those voices are not heard here does not necessarily indicate that some individuals and families do not suffer harm.

So, with all of that said, we have to decide as a Committee, is there high certainty of significant benefit, category A. Is there moderate certainty of significant benefit, Category B, or is there high

certainty of small benefit, C. And I would argue that there's probably fairly high certainty of significant benefit in the somatic findings. I think that you could make the argument that there's really moderate certainty of significant benefit in the somatic findings, because the evidence is challenging. I think it's -- I don't think anyone -- you could say that there's high certainty of small benefit if one considers neurologic outcome, somatic survival, and all of those things together, but I don't really think that that would be an accurate representation of the evidence.

I do think that we can say with fairly high certainty that there's moderate benefit in somatic findings, but that's not one of our options. So therefore, each Committee member is going to need to make a decision of whether the evidence that you've heard today and read in the report represents a significant benefit of compulsory population based newborn screening for MPS II.

And if I may have the next slide, Dr. DeLuca, and I, after careful consideration, feel that Category B of the decision matrix is most accurately reflects the evidence. There's moderate certainty that screening would

have a significant benefit. We think that this category gathers the uncertainty of the evidence in the most accurate way, although it's imperfect. May I have the next slide, please?

To address the readiness and feasibility question, I'm going to summarize what we've heard earlier and recognize that these are not -- that there may be some disagreement about this. But it appears to us that the newborn screening test are available and appropriate for high-throughput testing, and actually quite sensitive for the disorder. The proportion of patients awaiting a final diagnosis is less than ideal. There's just no way around that.

The proportion of true positive to all positive NBS results, which is close to one in ten, so about one in ten of the call outs will actually be diagnosed with the condition. That is certainly in the range of other conditions that are on the recommended uniform screening panel. So that is certainly the range of other conditions that are on the recommended uniform screening panel. So that does not appear to us to be a concern.

Second tier testing, I will add, we would say should be highly recommended to reduce false positives as much as we can. The additional cost of that second-tier test as a send out is dwarfed by the benefit of reducing the false positive rate in our opinion.

Readiness, again, I'd say this with some trepidation after our earlier discussion, but I think that the evidence suggests that most states could add screening in a reasonable period, one to three years, and we think that as states are adding MPS I and Pompe, MPS II can be added using similar approaches and should not add a significant burden to those states.

We do want to acknowledge that the marginal screening cost is higher than some -- than most other additions to the RUSP so far. And then we talked about this earlier, but it does appear to us that the evidence suggests that the follow-up resources are thought to be adequate for the demand for adding this particular condition. May I have the next slide, please?

So, we feel that the appropriate -- we feel that the developmental readiness falls into Category 2 and that there is high to moderate feasibility for implementation

over the next probably three to four years across the nation. And therefore -- if I may have the next slide -- we think that newborn screening for MPS II meets the criteria for matrix Category B2, the developmental readiness is to enact screening for MPS II is reasonable, and there's high or moderate evidence for feasibility of screening, testing and treatment in states newborn screening systems. May I have the next slide, please.

Therefore, our recommendation is that MPS II should be added to the recommended uniform screening panel as a core condition. Thank you.

CYNTHIA POWELL: Thank you, Dr. DeLuca, and Dr. McCandless. Thank you for serving as the Committee representatives on the ERG and for all the time and effort that you've devoted to this process and the development of your presentation.

COMMITTEE DISCUSSION

I'll now open it up to any questions or comments from Committee members. Cindy Hinton.

CINDY HINTON: Thank you, Dr. Powell. Cindy Hinton, CDC. Thank you for your summary, Drs. DeLuca, and

McCandless. I want to follow up with something that Dr. McCandless had brought up, and it was the statement about better survival rates with earlier treatment. Was that from the sibling studies or it may be the HOS, where did those particular data come from?

SHAWN MCCANDLESS: That's a great -- this is Shawn McCandless. That's a really good question that I think is more based on the expert opinion than it is on the actual data from those studies. It's also an assumption that because of the improvements in overall health and the cause of death often being respiratory and cardiac issues in these patients, that preventing those or delaying the decline in those symptoms is almost certainly going to have a significant impact on mortality.

I don't think it's fair to say from anything that we've seen that patients with the severe form of the disease are going to live normal lives and live to be late into adulthood with currently available therapies. I think that like many of the conditions that we consider for newborn screening, however, that we -- the patients that we get into treatment earlier now, who survive longer and better are also alive to benefit from potentially

better therapies that may be coming in the future. And I think the point has been made several times that we maximize that potential benefit for everyone by adding -- by getting a newborn screening diagnosis.

If I may just take a moment to pitch one of my favorite things, though, I think that you could also get almost all of that benefit from a much broader population based prenatal carrier testing program, and that I would encourage people who think about these kinds of things to not necessarily think that newborn screening is the only answer to solving public health issues related to genetic disorders, that carrier screening has been shown to be very effective for many disorders. I will now step off of my soapbox and shut up.

CINDY HINTON: Yes, thank you. Very helpful clarification, and I think, you know, a while ago there was a paper written on, you know, what makes something a public health screening versus clinical care. And you know, there is that option for something to be in clinical care. The evidence that has been presented is certainly pointing in the right direction, that early treatment will improve outcomes. And we've seen that in the sibling

studies. And I just want to reiterate what you and Dr. DeLuca said in your presentation, that we really -- that you know, researchers or people who are presenting cases for consideration really keep in mind, like this is what we need to know, you know. When we talk about evidence-based recommendations, like we need to have the evidence-based recommendations. And we see things that are promising, but we're working off of assumptions. You know, we're making a leap there that newborn screening itself is what is going to, you now, make that difference.

I really appreciate the thought that you all have put into this. Thank you.

SHAWN MCCANDLESS: Thank you. I'm sorry to jump in but I just want to respond very quickly to -- or it's not so much a response to what you said, Cindy, but just a -- Dr. Kemper said something that was really wise in some of our earlier conversations that I want to mention now, and that is that we were talking about other population based screening recommendations from the preventive services task force and things like that. And Dr. Kemper made the point that for newborn screening, it's basically all or nothing, because it's a compulsory program. Nobody

gets to talk to the family about newborn screening before it happens. It's just most families don't even realize it's happening until they get an abnormal result, and so it's we have to be really confident that the benefit is there. Whereas for other things, and the example would be carrier screening for these same conditions, that what that does is it gives the patient and the doctor an opportunity to have a meaningful discussion about what's best for their family and them as an individual. And it's -- so it puts a higher burden of responsibility on us when we're making a decision about compulsory newborn screening over sort of other recommendations about population-based screening, because in compulsory newborn screening, we remove that -- we remove that step of the patient and the doctor sitting down to talk about the potential benefits and the potential harms.

And Alex, if I've misstated that in some way or not reflected what you were really getting at, I apologize.

ALEX KEMPER: No, that was nice and I -- rarely do people call me wise, so I'll just leave it there.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: I definitely want Scott to go first. But no, actually, I'll just throw out there that I guess I just can't get over the weekly infusion, okay?

And so, I just want to -- I want some help in understanding how this works for people, and how this is going to work in newborn screening. We have a disorder where 60 percent of them -- 60 percent of the patients, if I heard that correctly, it's estimated, are going to have the more severe phenotype. There is no question that there is a net benefit to infusion. It will certainly make their lives longer and much more comfortable.

But I ask myself -- well, you know, they'll probably have a port placed. They'll probably be able to get this at home. It just seems like an unusual lifetime of treatment to present to people. And we've heard from people who have been so affected by this disorder, and for whom this treatment is a miracle. But I think we can also probably envision that there are -- there will be families for whom this will feel like a kind of assault, a kind of, you know, being suddenly thrown into this world that they probably had no expectation of it all, which is where the -- which is where Alex's wise comments about the program

and why part of the problem with newborn screening is we -- it's not designed for us to get consent. It's designed for us to look at those disorders that are so serious that the community has decided that we have to look for them for people instead of them making the decision. We've taken it out of their hands. We are saying that this disease must be treated. You know, it's so important we have to, at least, you know, go that route. And then I think over time there are many people who say well, we're not actually saying that it must be treated, we're saying that it's important that families have the decision to be able to treat it.

And I guess I would just throw it out there that for me, it seems like it might be hard for some families to hear what they're going to have to do, and that's why maybe that figure of families lost to follow up just sort of resonates with me, because I think that I might -- I think that I've seen families where that might be their reaction, to say well, thanks, and then not come back.

So, I was curious, Shawn and Jane -- I'm sorry, I'm more informal. I probably shouldn't be, but I really

am curious what you think about sort of the granularity of the actual care of these patients.

JANE DELUCA: Well, you know, I can say that it's interesting because when you think about public health screening and population screening, it really does come down to the individual family. In the end it comes down to this person who's gotten the abnormal result, that has to come in and be counseled. And I think that if this spreads and of course, if it's approved and more states roll out, we will seal these differences in terms of how families respond to this. I was shocked when I saw the five people who were lost to follow up, and I wonder if, you know, you take all these factors together, that this is a very daunting thing for a family to face, you know, a lifetime of treatment, and maybe it was too daunting for them. And I can think of instances for other disorders where this happened, you know, where people were lost to follow up and then just left, you know, the program.

So maybe what we need to do is to develop ways to be able to speak to people, therapeutically, and talk to these families therapeutically and meet them on their terms. You know, what do they understand? What are their

expectations? And I think what you're asking, Jennifer, is very legitimate. And certainly, we can speak to people in ways that will harm them if we aren't taking the care to meet people in terms of where they live when this happens.

SHAWN MCCANDLESS: If I could just add to that, thought. I would say at the end of the -- first off, your observation about the weekly treatment is right. I think you would have trouble finding a family who doesn't say that it's burdensome. My experience, though, and I think the experts would bear this out, is that you don't find too many families who don't -- who actually stop the therapy because of the burden until the child is deteriorated enough that they burden of the treatment outweighs the perceived benefit of the treatment. And that's when you have those -- that's an opportunity to have really meaningful discussions about what are your goals for your child?

I also think it's really important to say that I don't think that we're saying that you have to have treatment. And I know that's not what you were implying, Jennifer, but I think the evidence suggests from the

states that have already done this, that there is at least one family that opted not to start therapy right away. There were families who -- you know, there are choices that happen, and you can have the discussion.

I think that this is a case where the benefit of newborn screening is that a family gets to make the decision as early as possible to maximize the benefit of the therapy.

I think it is a little different though than maybe like PKU, where like if I met a family where we had just diagnosed with MPS II and they said we really don't think it's in our child's best interest to do enzyme therapy, I would say I think, you know, that's your decision to make. If I have a family with PKU who says I don't really think that a low phenylalanine diet is really in my child's best interest, I will call social services, because that's not acceptable. And I think -- I think the point you make, Jennifer, is that there is a difference in those two categories, and I'm not sure how to weigh that.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: I definitely want Kyle Brothers to go before me, because I know -- I think he's got more

pertinent things to say about what the discussion was before I changed a little bit, so I would like Kyle to go.

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: I hope, Scott, I don't disappoint you. Yeah, I must say I'm a primary care doctor and I'm skeptical of population level screening just because there -- you know, in the primary care setting we see the adverse effects of sort of the use of medical technologies out of proportion, you know. And you know, just the first thing we're taught in medical school is you don't do a test unless you know what you're going to do with the result, right?

So, and I strongly support evidence-based medicine, but I must say for an ultra-rare condition of this type, the evidence is about as good as we could reasonably expect. So, I agree with the conclusion of this as a B. And I think I'm supposed to be the ethicist for the Committee, so I'll just make one comment along those lines. I really am concerned about the effects on false positive families, and the way in which that distribution of harms and benefits might be unjust. But I am compelled by the scale of the benefit to these families

who get a true positive result. I don't want to deny that there are harms to the false positive families, but ultimately, it's, you know, a short-term inconvenience weighed against years of potential benefits that I really am quite convinced are significant based on the available evidence.

And then finally I'll just say there are many flaws that we've seen in the way the system works that would lead to newborn screening for this condition to be imperfect, right? And one of them is that some families are going to get lost to follow up. Maybe those families moved to a bigger -- you know, to another state in order to get better care. I mean, you know, we really can't say. Not all of those families maybe had a negative outcome. And obviously some of those kids may have gone on to not develop the condition and were unharmed.

But ultimately, there -- we can imagine other ways to pick up this condition early in life, either prenatally or through primary care settings, but fundamentally, those do not work well at this point in time, and I think we have opportunities in the decades ahead to really re-imagine how the healthcare system

operates, but at this point, newborn screening is the only way to recognize these benefits for families early in life. We're not going to get primary care providers to do some kind of test on every single child, so I just am compelled that I think this is the right thing to do for this particular condition, is to add it to the RUSP. So, thinks.

CYNTHIA POWELL: Scott Shone.

Scott Shone: So, it was the ethics perspective, Kyle, that I was hoping you would go before me. So, I do appreciate that.

Just a comment on that last comment you made about I don't think we'll get primary care providers to just do a test on every baby is really disheartening to think about, although it might be real, because we've talked in this group about other disorders that might not really make sense for newborn screening, but would be better in a primary care setting, and just to acknowledge that, Kyle, is really troubling to think about the future of getting things jammed on newborn screening that really might not be appropriate. I think we're already starting

to see it a bit. I'm not saying MPS II is it, but I think that others.

For Shawn, you know, I think as for Jane, there's a lot of likely and challenging, like just the sort of like buzz words in the presentation about where we go that that level of uncertainty gives me -- as people who know me well know uncertainty gives me angst. I plan everything, and so uncertainty gives me angst, and I talk about it with other disorders that are in the newborn screening panel.

But I wanted to hone-in a little bit on your comment around those who benefit differ from those who are harmed, and then the statement that low risk of treating -- there's a low risk of treating patients that will not benefit and get at sort of that risk of early treatment when not necessary. I don't know if I was clear on what my question was there, but can you just sort of help me understand what that all means, like who is really going to benefit most? It actually seems to me that while 60 percent will be severe, that 40 percent attenuated, who there's discrepancy on whether or not to treat them and that that Delphi process actually might be the ones who

benefit most from all of this. Is that -- did I totally miss that?

SHAWN MCCANDLESS: I think that -- this is Shawn McCandless, Committee member. I agree with you, Scott. I think that -- and I think the expert -- the technical expert panel, I think also made that point, that possibly the people who benefit the most are the people with the attenuated form who are going to have a likely -- likely going to have preserved cognition and live a long life. They're going to live a long life with better health, with better mobility, with fewer limitations on their life. so, I really do think that the -- that your point is an excellent one, that we didn't make very well in the summary, which is that the patients with the attenuated form really are the ones who are going to get the biggest benefit. There will be benefit in somatic symptoms for the most severe kids, but it probably doesn't change the ultimate outcome for those individuals by a lot. Their life will be better. It will probably be a little longer, but the outcome is likely to be the same, just a little bit delayed, whereas for the attenuated group, it will be much bigger.

I think that your observation about the use of the term, likely, in the summary is really the reflection that Kyle alluded to of the complexity of getting meaningful data for a really rare disorder from the medical literature.

You know, I hope that we'll all learn from this. I think I will. In the future when I'm working with colleagues to write a case report, you can bet I'm going to be saying, you know what, we need to compare apples to apples. We need to go through every case. We need to go back and ask every one of these physicians to say where was this kid in this measure at age three, at age five, at age eight? We need to have all of our ducks in a row when we publish these data. That has not been the standard in the past. It needs to be going forward.

SCOTT SHONE: So, you read my mind in my last comment, Shawn, who is what you just described is the thing we talk about all the time for years and years and years, and that's long-term follow-up. And you know, I got a little frustrated two meetings ago that we talk about this a lot, over and over again, and here is another example. We don't have it.

And so, Jane, you said something to the effect of -- I actually don't remember what you said, because I was -- you said we'll see that data. And I'm like, are we? Will we see that data? Will we see that data, and I put long term follow-up? You know, I don't -- I don't have the faith right now in the newborn screening system that a year or two from now, say all those states who are about to implement MPS I say it makes sense to validate MSP II at the same time and do them both at the same time and we have a sudden surge of both. Are we all confident that we're going to get that data? I'm not. And so -- and the question I have -- I guess not question, but the comment, you know, Kyle said we are where we are, right? We're not going to get any better. And I agree with that. But you know, I'll just leave it at I think that there's a -- we are -- Dr. Powell, you said, you know, we're looking at what about multiple disorders coming? I think we need to figure out this data piece like really quickly, because I think Sabra Anckner said it, three's hundreds of millions of dollars that come into infectious disease, and we need to take advantage of that for rare disease. And that's -- thanks.

SHAWN MCCANDLESS: You're preaching to the choir, Scott, on that. I think we would be remise, though, if we didn't acknowledge the good work that the long-term follow-up working group has made and the progress they've made in recommendations, and the fact that HRSA has been responsive to that and is investing -- has made investment in improving long term outcome -- or long term follow up and outcome assessment. Are we where we need to be? No. Are we getting better? Too slowly. But we're moving in the right -- it seems to me we're moving in the right direction, and I want to acknowledge HRSA's role in that.

CYNTHIA POWELL: Chanika.

CHANIKA PHORNPHUTKUL: Hi, this is Chanika Phornphutkul. I just want to go back to one of the comments about the -- you know, sort of we are thinking of many conditions that could be quote, unquote, screened or picked up later in life, and you know, relying on primary care. I think one of the points that Dr. Kemper actually pointed out really nicely was that you compared the early treatment, you know, before six months. And I recognize the limitation of comparing the siblings, but at least for this specific condition, I do feel that we have

information of a potential benefit or likely benefit for the early institution of treatment. So, I think that was one of the points that I want to make to this group.

Second, in terms of the long-term treatment -- long term follow-up, you know, I'm a new member, so I really don't know what else have been discussed before, but I do think that from other professional society, I think Max Muenke is on here, Dr. Berry is on here, that really falls onto us as professionals to continue or, you know, do a better job. I know that it's not going to address what the question we have today, but also, I think those are something that's being done. I think we don't have the benefit of SMA when it's much more common, or CF where, you know, it's much more common to have this large powerful data. But I think we can get there eventually. Thank you.

VOTE ON WHETHER OR NOT TO RECOMMEND MPS II FOR INCLUSION ON THE RECOMMENDED UNIFORM SCREENING PANEL

CYNTHIA POWELL: Thank you. All right, I'm not seeing any other hands raised. So, I think we're ready to move forward with a motion. Would anybody be willing to

make a motion as to whether to accept or not accept the recommendation, both including the rating and whether to recommend MPS II to the Secretary or not, any Committee member.

KYLE BROTHERS: This is Kyle Brothers. I move that we accept the recommended rating of B2 for this condition and that we recommend that the Secretary add it to the RUSP.

CYNTHIA POWELL: Is there a second?

UNIDENTIFIED SPEAKER: I second.

CYNTHIA POWELL: Are there any additional comments before we vote?

SHAWN MCCANDLESS: This is Shawn McCandless. Can I -- Kyle, would it be okay if I modified the recommendation to say that it should be added to the RUSP as a core condition?

KYLE BROTHERS: Sorry, yes. Thank you.

SHAWN MCCANDLESS: Thank you.

CYNTHIA POWELL: Cindy Hinton.

CINDY HINTON: Yes. I know that in the past the Committee has asked for -- or somehow like people have come back to report, how is this going? I don't know how

to, you know, emphasize more this need for the data. And that may not be in this particular point right here. So, I just -- it's more like a point of clarification for how the Committee operates.

CYNTHIA POWELL: Yes. Well, for SMA, the Secretary did ask the Committee to do a follow-up evaluation a few years or within -- I can't remember, Alex, how many years, two or three years after that was approved. And that is the plan for all of the conditions on the RUSP. So that is something that's planned and also the Secretary may ask for that. Jennifer.

JENNIFER KWON: This is Jennifer Kwon. Just to echo what Cindy just said, I think that it would be really interesting to have MPS I and maybe also what, you know, the follow-up on MPS II at the same time, just because it has been a few years since MPS I was recommended. And as I said, it does seem like the uptake has been a little bit slow. And I think that it's -- I think that there is information that we just aren't hearing because of the nature of these rare diseases and how they get presented to us. It's also in the nature of these rare diseases and their presentation that what we read in the medical

literature is a certain point of view. And so, I think it's only with population-based screening that we see the broader picture, and that will be helpful for, you know, informing how we might decide in the future.

CYNTHIA POWELL: Thank you. All right, I don't see any other hands. So, the motion is to approve the B2 rating and to recommend that MPS II be added to the RUSP as a core condition. Do any Committee members have a conflict of interest regarding this vote and need to recuse themselves?

Are there any abstentions? All right, I will now call each member's name and you will please answer yes or in favor if you are in favor of the motion. Or if you are not in favor of the motion, please state not in favor. Kyle Brothers.

KYLE BROTHERS: In favor.

CYNTHIA POWELL: Cindy Hinton, representing CDC.

CINDY HINTON: In favor.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: In favor.

CYNTHIA POWELL: Kellie Kelm, representing FDA.

KELLIE KELM: In favor.

CYNTHIA POWELL: Jennifer Kwon.

JENNIFER KWON: Not in favor.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: In favor.

CYNTHIA POWELL: Kamila Mistry.

KAMILA MISTRY: In favor.

CYNTHIA POWELL: Melissa Parisi, NIH.

MELISSA PARISI: In favor.

CYNTHIA POWELL: Chanika Phornphutkul.

CHANIKA PHORNPHUTKUL: In favor.

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

SCOTT SHONE: In favor.

CYNTHIA POWELL: Michael Warren representing HRSA.

MICHAEL WARREN: In favor.

CYNTHIA POWELL: So, the outcome of the vote is that the condition is recommended for addition to the RUSP with a B2 rating. The Committee has voted in favor of recommending adding MPS II. 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 ERG, and the Technical Expert Panel.

And definitely this involved a lot of time and effort. Thank you all for your thoughtfulness on this and your dedication to the Committee.

ADJOURNMENT

CYNTHIA POWELL: And this will bring the end of Day 1 and I look forward to reconvening tomorrow at 10:00 a.m. Eastern time. Thank you.