The Advisory Committee on Heritable Disorders in Newborns and Children

Virtual Meeting

10:00 a.m.

Tuesday, November 9, 2021

Attended Via Webinar

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Reported by Garrett Lorman

Committee Members

Mei Baker, MD
Professor of Pediatrics
University of Wisconsin School of Medicine and Public Health
Co-Director, Newborn Screening Laboratory
Wisconsin State Laboratory of Hygiene

Jeffrey P. Brosco, MD, PhD
Professor of Clinical Pediatrics, University of Miami
Title V CYSHCN Director, Florida Department of Health
Associate Director, Mailman Center for Child Development
Director, Population Health Ethics, UM Institute For Bioethics and Health Policy

Kyle Brothers, MD, PhD
Endowed Chair of Pediatric Clinical and Translational Research

Committee Members - continued

Associate Professor of Pediatrics University of Louisville School of Medicine

Jane M. DeLuca, PhD, RN
Associate Professor
Clemson University School of Nursing

Shawn E. McCandless, MD
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Head, Section of Genetics and Metabolism
University of Colorado Anschutz Medical Campus
Children's Hospital Colorado

Cynthia M. Powell, MD, FACMG, FAAP (Chairperson)
Professor of Pediatrics and Genetics
Director, Medical Genetics Residency
Program Pediatric Genetics and Metabolism
The University of North Carolina at Chapel Hill

Committee Members - continued

Annamarie Saarinen
Co-founder
CEO Newborn Foundation

Scott M. 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
Senior Advisor
Child Health and Quality Improvement

Centers for Disease Control & Prevention
Carla Cuthbert, PhD
Chief
Newborn Screening and Molecular Biology Branch
Division of Laboratory Sciences

Ex-Officio Members - continued

National Center for Environmental Health

Food & Drug Administration
Kellie B. Kelm, PhD
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Division of Chemistry and Toxicology Devices

Health Resources & Services Administration
Michael Warren, MD, MPH, FAAP
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Maternal and Child Health Bureau

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Melissa Parisi, MD, PhD
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Ex-Officio Members - continued

Designated Federal Official

Mia Morrison, MPH

Genetic Services Branch

Maternal and Child Health Bureau

Health Resources and Services Administration

Organizational Representatives

American Academy of Family Physicians

Robert Ostrander, MD

Valley View Family Practice

American Academy of Pediatrics

Debra Freedenberg, MD, PhD, FFACMG, FAAP

Medical Director

Newborn Screening and Genetics

Texas Department of State Health Services

American College of Medical Genetics & Genomics

Maximilian Muenke, MD, FACMG

Organizational Representatives - continued

Chief Executive Officer
Maryland Department of Health Maternal and Child Health Bureau

American College of Obstetricians & Gynecologists
Steven J. Ralston, MD, MPH
Chair, OB/GYN
Pennsylvania Hospital

Association of Maternal & Child Health Programs
Jed Miller, MD
Director, Office for Genetics and People with Special Care Needs
Maryland Department of Health Maternal and Child Health Bureau

Association of Public Health Laboratories
Susan M. Tanksley, PhD
Manager, Laboratory Operations Unit
Texas Department of State Health Services

Organizational Representatives - continued

Association of State & Territorial Health Officials

Christopher Kus, MD, MPH
Associate Medical Director
Division of Family Health
New York State Department of Health

Association of Women's Health Obstetric and Neonatal Nurses

Shakira Henderson, PhD, DNP, MS, MPH, RNCNIC, IBCLC
Vice President, Research Officer University of North Carolina Health
Board Director, Association of Women's Health, Obstetric & Neonatal Nurses

Child Neurology Society

Jennifer M. Kwon, MD, MPH, FAAN
Director, Pediatric Neuromuscular Program
American Family Children's Hospital

Organizational Representatives - continued

Professor of Child Neurology, University of Wisconsin School of Medicine & Public Health

Department of Defense
Jacob Hogue, MD
Lieutenant Colonel, Medical Corps, US Army
Chief, Genetics, Madigan Army Medical Center

Genetic Alliance
Natasha F. Bonhomme
Vice President of Strategic Development

March of Dimes
Siobhan Dolan, MD, MPH
Professor and Vice Chair for Research
Department of Obstetrics & Gynecology and Women's Health
Albert Einstein College of Medicine and Montefiore Medical Center

Organizational Representatives - continued

National Society of Genetic Counselors

Cate Walsh Vockley, MS, CGC

Senior Genetic Counselor Division of Medical Genetics

UPMC Children's Hospital of Pittsburgh

Society for Inherited Metabolic Disorders

Georgianne Arnold, MD

Clinical Research Director, Division of Medical Genetics

UPMC Children's Hospital of Pittsburgh

C O N T E N T S

P R O C E E D I N G S

WELCOME AND ROLL CALL

CYNTHIA POWELL: Good morning, everyone. I'll now call to order the fourth meeting in 2021 of the Advisory Committee on Heritable Disorders in Newborns and Children. I'm Dr. Cynthia Powell, Committee chair. We're going to begin by taking roll.

First our Committee Members.

Representing the Agency for Health Care Research and Quality, Kamila Mistry.

KAMILA MISTRY: Here.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Here.

CYNTHIA POWELL: Jeff Brosco.

JEFF BROSCO: Here.

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: Here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

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

Cuthbert.

CARLA CUTHBERT: I'm here.

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

KELLIE KELM: Here.

CYNTHIA POWELL: Representing HRSA today, Joan Scott.

JOAN SCOTT: Here.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Here.

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

MELISSA PARISI: Here.

CYNTHIA POWELL: And Cynthia Powell. I'm here.

Annamarie Saarinen.

ANNAMARIE SAARINEN: Here.

CYNTHIA POWELL: And Scott Shone.

SCOTT SHONE: Here.

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

ROBERT OSTRANDER: Here.

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

DEBRA FREEDENBERG: Here.

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

MAXIMILIAN MUENKE: Here.

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

(No audible response)

CYNTHIA POWELL: From the Association of Maternal and Child Health Programs, Jed Miller.

JED MILLER: Here.

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

(No audible response)

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

(No audible response)

CYNTHIA POWELL: From the Association of

Women's Health, Obstetric, and Neonatal Nurses, Shakira Henderson.

SHAKIRA HENDERSON: Present.

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

MARGIE REAM: Here.

CYNTHIA POWELL: 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 of Inherited Metabolic Disorders, Georgianne Arnold.

(No audible response)

CYNTHIA POWELL: Okay. Thank you.

I'll now turn things over to Mia Morrison, our Designated Federal Official.

OPENING REMARKS AND COMMITTEE BUSINESS

MIA MORRISON: Thank you, Dr. Powell.

Next slide.

(Slide)

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

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.

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MIA MORRISON: According to FACA, all Committee meetings are open to the public. If the public wishes to participate in the discussion, the procedures for doing so are published in the Federal Register and/or announced at the opening of the meeting.

For the November meeting, in the Federal Register notice we said that there would be a public comment period. Only with advance approval of the chair or Designated Federal Official, public participants may question Committee Members or other presenters. Public participants may also submit written statements. Also, public participants should be advised that Committee

Members are given copies of all written statements submitted by the public.

As a reminder, it is stated in the FRN as well as the registration website that all written public comments are part of the official meeting record and are shared with Committee Members. Any further public participation will be solely at the discretion of the chair and the DFO.

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

CYNTHIA POWELL: Thank you, Mia.

Before we begin today's agenda, I'd like to acknowledge that this will be the last Advisory Committee meeting for Dr. Mei Baker, Dr. Jeffrey Brosco, and Annamarie Saarinen, whose terms will end in December.

Dr. Baker, as director of an innovative state newborn screening laboratory, the Committee has benefited from your expertise and insight, as has the Laboratory Standards and Procedures Workgroup on which you have served.

Dr. Brosco, your expertise as a

pediatrician and bioethicist and thoughtful commentaries, have enlightened many Committee discussions. We also acknowledge and thank you for your service as chair of the Long-Term Follow-Up Workgroup and member of the Nomination and Prioritization Workgroup.

Ms. Saarinen, as a parent advocate helping to lead the effort to add critical congenital heart disease newborn screening to the RUSP prior to your service on the Committee, your voice has been extremely important to the work of this Committee in the follow-up and treatment work.

Each of you has dedicated countless hours to attend Committee meetings, contributed to Committee products, participated on workgroups, and applied your in-depth subject-matter expertise to Committee deliberations and decisions.

On behalf of HRSA and the Advisory Committee, we thank you for your outstanding service and contributions to the Committee and the field of newborn screening.

If we were in person, I would now present you with a certificate and letter of appreciation from the Acting Administrator of HRSA, Diana Espinosa. Please look for these tokens of our gratitude in the mail.

I'd now like to open the floor to Annamarie Saarinen, Dr. Baker, and Dr. Brosco if they would like to say a few words.

I think, Annamarie, you're first on the list.

ANNAMARIE SAARINEN: That's unfair. I wanted to go after somebody and gather my thoughts.

CYNTHIA POWELL: Sorry.

(Laughter)

ANNAMARIE SAARINEN: Thank you so much, Dr. Powell, for the kind acknowledgements.

I was telling some colleagues that this was going to be our last meeting on this esteemed Committee, and I had mixed emotions about it.

Because it has been truly one of the greatest privileges, I think of my adult life to

have been appointed and had this chance to serve and learn from the colleagues in this group, to hear from and represent the patient and parent community.

I am so grateful that HRSA and this workgroup always considers and goes out of its way actually to ensure it's represented as part of the process of reviewing and potentially adding new conditions to the panel that impacts every baby in our country.

So, I just want to express my sincere gratitude for the opportunity. And I think on behalf of my family and my daughter, I hope the journey we went on resulted in some additional benefit for public health in this country. And I know this will happen for others, moving forward.

So, I will watch and participate as much as I can, moving forward because newborn screening will always be very, very near and dear to my heart. So, thanks for the opportunity to say a few words.

CYNTHIA POWELL: Thank you.

Dr. Mei Baker.

MEI BAKER: Well, I knew that, right? But I couldn't describe what's in my emotion now. It was really such a great honor to serve. And I think, Annamarie, as you mentioned even more emotional. I just want to say again thank you for all the kind words, and I'm really enjoying very much. I think the effort is totally, totally worth it. And also, I learned so much from my fellow Members.

So, thank you to everybody. I'm not done with NBS so, I will see you all later. Thank you.

CYNTHIA POWELL: Thank you.

Dr. Jeff Brosco.

JEFF BROSCO: Well, as Annamarie and Mei said, it's a wonderful honor to be part of this group and a truly awesome responsibility to make the decisions that we do as a group.

And the thing that I think is the most impressive about newborn screening is that, amidst all the madness in the world, we get to be rational, evidence-based, seeking the best

interests of everyone. It's a transparent process. It's really extraordinary. It's a unique part of medicine and health care and science in the United States.

And to be with such incredibly intelligent and dedicated people has been just wonderful. I think that we all feel that way.

Not only is it rare for us to be so logical and evidence-based, but it's also about building equity. It's a universal program and reduces disparity in our community.

So, whenever someone grouses about how government can't do anything, I say, "Well, what do you know about newborn screening?" We just talk a little bit about what happens in each state. And they say, "Oh, I didn't know we could do that." I say, "Yeah, we do that."

The few years that I had on the Committee I've really enjoyed. And one thing I've tried to impress is the public health perspective. The idea that while -- you guys are probably tired of my saying this. But in Florida right now, I put

on my Title 5 hat in MCHB, and I think about the 400,000 children with developmental and behavioral disorders, only half of whom get any treatment. So, 200,000 kids right now are not getting any treatment.

And you could extend this to newborn screening, right, because we know that many of the children identified by newborn screening don't get the high-quality treatment or follow-up that they need.

So, as we move forward, as you guys move forward as a Committee, I hope you keep that public health perspective. I always think about how we are making sure that the work we do in newborn screening gets extended to everyone for as long as possible.

Thank you, guys. It's been a lot of fun, and I'm really going to miss the tuna melts and sweet potato fries from the HRSA cafeteria. It's the hardest part of this process.

(Laughter)

CYNTHIA POWELL: Thank you.

Once again, thank you all for your service. May each of you continue then to have a lasting impact on newborns and their families across the nation.

Now we can go to the next slide.

(Slide)

CYNTHIA POWELL: As you may recall, in July 2021, HRSA received the nomination package for Krabbe Disease, or globoid cell leukodystrophy. Krabbe disease is both a leukodystrophy and a lysosomal storage disorder and was first nominated to the Advisory Committee in 2007. It went through evidence-based review.

However, in 2009, the Committee voted to not recommend the addition to the recommended uniform screening panel. The Nomination and Prioritization Workgroup is reviewing the nomination package for Krabbe disease and will keep both the nominators and the rest of the Committee informed of next steps.

I would also like to inform the Committee that on October 3rd, the National CMV Foundation

submitted a RUSP nomination package for Congenital Cytomegalovirus, or cCMV. The National CMV Foundation initially submitted a RUSP nomination package for cCMV in March of 2019.

At that time, HRSA conducted a review for completeness and asked the nominators to provide additional information missing from the package. HRSA is conducting the review for completeness on the resubmitted packets and will continue to update the nominators and Committee of next steps.

Today the Committee will vote on whether or not to approve proposed updates to the Committee's nomination, evidence-based review, and decision-making process. The proposed changes are intended to strengthen the Committee processes for reviewing conditions but will not increase burden for nominators or advocates.

As a reminder for groups that may be the process of developing condition nomination packages, if approved by the Committee these processes will not go into effect until calendar year 2022.

If your organization is working on a condition nomination package and you are planning to submit in early 2022, please contact the Committee's Designated Federal Official, Mia Morrison, who can provide you with additional guidance. Mia and I are available to provide technical assistance to nominators.

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(Slide)

CYNTHIA POWELL: The Education and Training, Follow-Up in Treatments, and Laboratory Standards and Procedures Workgroups will convene today from 3:00 to 4:30 p.m. Eastern time. The Zoom links for the workgroups will be posted on the workgroup's tab of the ACHDMC meeting registration website. Please note this is not the same as the Committee's website.

I will also have this web address available at the end of the meeting today. We will provide instructions for accessing the Zoom links for the workgroup meetings again before we adjourn for the day.

Next slide.

(Slide)

CYNTHIA POWELL: I have asked the workgroups to continue the conversation on challenges facing the newborn screening workforce. As you recall, during the last two meetings we heard from critical members representing those who are part of the newborn screening system both on the laboratory side, the short-term follow-up, as well those with long-term follow-up.

I'd like to continue with those discussions, and so I've asked the workgroups to continue the conversation on challenges facing the newborn screening workforce strategies to address workforce-related gaps and assess potential ways the Committee could support meeting current and future needs of the newborn screening workforce.

I've assigned the following questions to the workgroups. For all workgroups, please discuss the following questions:

Should the Committee consider the availability of follow-up experts (clinical,

follow-up, public health, laboratory side, etc.) when reviewing a new condition nominated to the RUSP? How could that information be collected? And what role could the Committee play in calling attention to identified shortages of follow-up experts?

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(Slide)

CYNTHIA POWELL: Specifically for the Education and Training Workgroup, where are the major gaps in newborn screening workforce education? Do Education and Training Workgroup members have additional recommendations on resources or training opportunities that support addressing shortages in the newborn screening workforce? How could those resources be expanded to further strengthen the newborn screening system?

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(Slide)

CYNTHIA POWELL: For the Follow-Up and Treatment Workgroup, what are the key workforce-

related challenges impacting access to short- and long-term follow-up, including treatment for individuals and families identified with conditions on the RUSP? Are there examples of workforce innovations that have supported access to short- and long-term follow-up care?

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(Slide)

CYNTHIA POWELL: For the Laboratory Standards and Procedures Workgroup, at the August 2021 ACHDNC meeting, the Association of Public Health Laboratories outlined challenges facing the NBS laboratory and follow-up workforce and resources that have been used to address those challenges.

Are there other resources that have been used at the state or national level to address laboratory workforce challenges? How could those resources be expanded to further strengthen the newborn screening laboratory workforce?

And also, the workgroups are certainly free to discuss other things that they would like,

and we're happy to once again engage the workgroups for discussion. We do appreciate all members of the workgroups and the input that they have in providing feedback to help.

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(Slide)

CYNTHIA POWELL: Thank you to the Committee and organizational representatives for reviewing the August 2021 meeting summary. We received one correction that is not reflected in the version that Committee Members received from the briefing book.

On page 21 in the third bullet of the Committee Discussions section that states, "A Committee Member requested that Dr. Shallon addressed the interface between lab work and follow-up," the correction is to strike "any number" and replace with "organizational representative."

Are there any other corrections or additions before the Committee votes?

(No audible response)

APPROVAL OF MINUTES

CYNTHIA POWELL: Hearing none, do I have a motion to approve the Minutes for the August 2021 ACHDNC meeting?

UNIDENTIFIED FEMALE VOICE: So, moved.

CYNTHIA POWELL: Is there a second?

UNIDENTIFIED FEMALE VOICE: Second.

CYNTHIA POWELL: All right. I will now call each Committee Member's name. Please state whether you approve or disapprove the minutes or if you're abstaining.

Mei Baker.

MEI BAKER: Approve.

CYNTHIA POWELL: Jeff Brosco.

JEFF BROSCO: Approve.

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: Approve.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: Approve.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Approve.

CYNTHIA POWELL: Kellie Kelm.

Kellie KELM: Approve.

CYNTHIA POWELL: Shawn McCandless.

SHAWN MCCANDLESS: Approve.

CYNTHIA POWELL: Kamila Mistry.

KAMILA MISTRY: Approve.

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Approve.

CYNTHIA POWELL: Cynthia Powell; I approve.

CYNTHIA POWELL: Annamarie Saarinen.

ANNAMARIE SAARINEN: Approve.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Approve.

CYNTHIA POWELL: Joan Scott.

JOAN SCOTT: Approve.

So, the minutes are approved. Thank you.

Next slide.

(Slide)

CYNTHIA POWELL: So, here's the agenda for the November 2021 meeting. The Committee will meet today from 10:00 a.m. to 2:00 p.m. Eastern time. First on the agenda for today, November 9th, Dr. Alex Kemper and Dr. Lisa Prosser will

provide the Phase 2 update on the evidence-based review for mucopolysaccharidosis type II.

CYNTHIA POWELL: Next, I will review the Immediately Actionable Committee updates to the condition nomination form, evidence-based review, and decision matrix guidance. Afterward, the Committee is scheduled to vote on these updates.

Following the vote, I will briefly recap several of the key issues identified for future consideration through the Committee's review of its processes.

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(Slide)

CYNTHIA POWELL: Please note that there will be a slight schedule change and we will break from 12:15 to 1:00 p.m. Eastern time. After returning from the break, we will receive public comments from three individuals. They are Zhanzhi (Mike) Hu, MPS II; Niki Armstrong, who will provide an update on newborn screening for Duchenne muscular dystrophy; and Dylan Simon on behalf of the EveryLife Foundation for Rare

Diseases.

During our last session of the day, Dr. Melissa Rasper, from RTI International, will provide an overview of the HRSA newborn screening portfolio evaluation.

We will end the first day of the meeting at 2:00 p.m. Eastern time. As I mentioned earlier, the Education and Training, Follow-Up and Treatment, and Laboratory Standards and Procedures Workgroups will meet from 3:00 p.m. to 4:30 p.m. Eastern time.

Next slide.

(Slide)

CYNTHIA POWELL: The Committee will reconvene tomorrow, Wednesday, November 10, from 10:00 a.m. to 1:15 p.m. Eastern time. We'll start with the Phase 1 update on the evidence-based review for guanidinoacetate methyltransferase deficiency, or GAMT deficiency.

Afterward, our workgroup chairs will update the Committee on workgroup activities, and discussions, followed by a short break.

And our last session of the meeting will be on newborn screening pilot studies with presentations by Dr. Melissa Wasserstein, from ScreenPlus in New York; and Dr. Don Bailey, from Early Check in North Carolina.

I'll now turn things back over to Mia.

MIA MORRISON: Thank you.

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(Slide)

MIA MORRISON: Now I'll go over some guidance for participating in today's webinar. For members of the public, audio will come through your computer speakers. So please make sure to have your speakers turned on. If you can't access the audio through your computer, you may dial into the meeting using the telephone number in the email with your Zoom link.

For Committee Members, audio will come from your computer speakers, and you'll be able to speak using your computer microphone. If you cannot access the audio and microphone through your computer, you may dial into the meeting using

the telephone number in the email with your user-specific Zoom link.

Please speak clearly and remember to state your first and last names in order 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 discussions, Committee Members and org reps should use the raise-hand feature if you would like to make comments or ask questions. Simply click on the "participant" icon and choose "raise hand." Please note that, depending on your device or operating system, the raise-hand feature may be in a different location.

To trouble-shoot, the webinar instructions page in your brief can help.

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MIA MORRISON: To enable closed captioning, please select the "closed captioning"

icon from your Zoom taskbar. From that menu, then select "Show subtitles."

Thank you.

Dr. Powell.

CYNTHIA POWELL: Thank you, Mia.

At the May 2021 meeting, the Committee voted to move mucopolysaccharidosis type II, or MPS II, to full evidence-based review. And this was assigned to the external Evidence-Based Review Group, or ERG. From May, the Committee has nine months to complete the evidence-based review and vote on whether or not to recommend MPS II for addition to the Recommended Uniform Screening Panel. The Committee received the Phase 1 update for the evidence-based review in August.

Today, Dr. Alex Kemper, ERG Lead and Dr. Lisa Prosser, who is a member of the ERG, will provide the Phase 2 update.

Committee Members, please note that in February 2022, the Committee is scheduled to vote on whether or not to recommend MPS II for inclusion in the RUSP.

Before turning it over to Dr. Kemper and Dr. Prosser, I would like to introduce them. Dr. Kemper is the Division Chief of Primary Care Pediatrics at Nationwide Children's Hospital, and Professor of Pediatrics at the Ohio State University College of Medicine.

He completed his pediatric residency training at Duke University, followed by combined fellowship training in health 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, Pediatrics.

Lisa Prosser, Ph.D., is the Marilyn Fisher Blanch Research Professor of Pediatrics and Director of the Susan B. Meister Child Health Evaluation and Research Center at the University of Michigan. Dr. Prosser also holds an adjunct faculty appointment at the Harvard School of

Public Health.

Her research focuses on measuring the value of childhood health interventions using methods of decision sciences and economics. Dr. Prosser's research evaluating the cost-effectiveness of vaccination programs has been used in setting national vaccine policy for children and adults.

Dr. Kemper, I will turn it over to you.

MUCOPOLYSACCHARIDOSIS TYPE II EVIDENCE-BASED REVIEW: PHASE 2 UPDATE

ALEX KEMPER: Thank you very much, Dr. Powell.

And before I get into this presentation, I just want to give an additional thanks to Annamarie, Mei, and Jeffrey. Their work with us has really been invaluable. They helped improve the process and the rigor with which we do our work. So, I just wanted to publicly thank them before they rotate off.

So as Dr. Powell mentioned, this is the interim update of our review. And in February we will be bringing things to conclusion for the

Advisory Committee Group.

Next slide, please.

(Slide)

ALEX KEMPER: So, I'm just going to leave this up for a second to thank members of our team. I'm incredibly lucky to work with smart and very dedicated individuals. I'd also like to thank Jane DeLuca and Shawn McCandless for serving as the Committee liaisons and helping prepare this presentation, making sure that we ask the difficult questions that need to be asked as we do our work.

Next slide, please.

(Slide)

ALEX KEMPER: As with all of the projects in the review process, we assembled technical expert panel members. This is a list here of the individuals that have been helping us through. Again, this evidence review work wouldn't be possible without having these individuals help put the findings into perspective.

Next slide, please.

(Slide)

ALEX KEMPER: So again, the objective today is to update things with where we are and highlight some key findings. I'm going to go back and forth between some things that we found in the published literature, the unpublished literature from talking to states that are doing newborn screening.

I'm also, as I talk through, I'm going to identify gaps in the body of evidence that's out there and be proposing solutions. At that point I'm going to bring in my colleague and friend, Dr. Lisa Prosser, who's going to talk about the implications of this for the modellings that we do to estimate the impact in newborn screening on the population of newborns who are being screened.

And then, of course, we're going to end with next steps as we move toward the February vote.

Next slide, please.

(Slide)

ALEX KEMPER: So, I'm just going to touch

base and so on, and remind people of things that we talked about at the last meeting, so MPS II is an X-linked inborn error metabolism caused by the deficiency of this specific enzyme that leads to the accumulation of glycosaminoglycans or GAGs, as you'll be hearing me talk about.

There are many mutations in the IDS gene, including many private mutations. Based on published reports that clinically detect a prevalence and, as you all know, once newborn screening begins there's often a discrepancy between what has been recognized and what's found through newborn screening.

But the clinically detected prevalence is this wide range of between 0.2 and 2.5 per 100,000 live births, depending on the population you look at, and the particular study in terms of the way that it's done.

As we also mentioned before, there are different ways to break up the phenotype of MPS II. The one that I am going to be using preferentially today is attenuated and severe. We

talked about the differences between that and the neuronopathic/non-neuronopathic classifications before. But simply because so many publications use an "attenuated" and "severe," I'm going to stick with that.

About two-thirds of cases, based on clinical and detected prevalence, fall into a severe category. Again, I want to remind everyone based on what was said at the last presentation that "attenuated" does not mean "benign." It is just that it doesn't have the same degree of CNS involvement.

And then some who have screened positive will have pseudodeficiency and I'll talk about that again later.

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(Slide)

ALEX KEMPER: The severe form is associated with progressive multi-organ and joint involvement, cognitive impairment, and even regression. Diagnosis is typically in early childhood for clinically detected cases between 18

and 36 months with mortality in the teens or 20s in the absence of treatment, which consists of enzyme replacement therapy.

The attenuated form has regular diagnoses, which could be a little bit later again. Some of this gets into classification, but it's typically described as a little bit later in childhood. Again, it has the same type of progressive multi-organ involvement, but no CNS impairment. And some individuals would be attenuated when these come into adulthood again. You know, this is a spectrum condition.

Next slide, please.

(Slide).

ALEX KEMPER: The phenotype is not typically predictable at the time of diagnosis unless you have peculiar mutations. And the phenotypic prediction is not typically possible for the private mutations, and I talked about that there are a large number of those.

Screening is based on MS/MS or fluorometry, and diagnosis is based on confirmed

low enzyme activity and also measuring GAGs levels to rule out pseudo-deficiencies. Those are individuals who look like they have low enzyme activities, but then had elevated GAGs. Genotype could be helpful in, of course, ruling out other related conditions like multiple sulfatases.

There is targeted treatment available for MPS II. There are enzyme replacement therapies, which is the predominant form of the treatments that is used. As I talked about last time, there's also hematopoietic stem cell transplantation. The challenge is with the enzyme replacement therapy not getting into the CNS for individuals with severe neuronopathic form of MPS II.

Next slide.

(Slide)

ALEX KEMPER: Here we go. So, this is a photo-diagram of the articles that we have identified through the published literature. And the bottom line is there are a little over 130 studies that we are evaluating as part of this

evidence review.

Next slide.

(Slide)

ALEX KEMPER: I'm just going to touch base on some things I think are particularly relevant to the Committee's understanding as we move forward toward the February vote. And a lot of what I'm going to point out today comes from the Hunter Outcome Survey, which is a registry of individuals with MPS II or Hunter's Syndrome.

The first thing that I just want to illustrate with this slide is these compares treated to untreated individuals by treating that we're referring to, enzyme replacement therapy.

And the few things that I want to point out, one, is that there is a relatively large number of individuals in the Hunter Outcome Survey, which has been very helpful in terms of understanding the impact of therapy.

And, you know, the key take-home from this slide as well is that enzyme replacement

therapy is an effective therapy. We know that. And still one of the questions that's going to come up as I go through this particular presentation is the benefits of earlier pre-symptomatic treatment versus clinically detected, you know, when cases are clinically detected.

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(Slide).

ALEX KEMPER: This slide also comes from the registry, and it breaks systems affected by MPS II and age of onset, which can be variable. So, you can just see that there's a sort of timing of one end, the symptoms associated with early disease involvement which MPS II went into impacts. But again, this slide doesn't get to the benefits of early treatment, which we're going to move into in a moment.

Next slide, please.

(Slide).

ALEX KEMPER: So, when you look across the studies, there is a wide range of treatment outcomes that are described. And the ones that

are bolded are the key ones that we found recorded in multiple studies. So, things like respiratory failure, cardiac involvement, liver volume involvement, development, ability to ambulate, and overall enduring physical features and urinary GAG levels.

The ones that aren't bolded are things that we found reported and things that we were particularly interested in looking at but are harder to summarize across studies.

Next slide.

(Slide)

ALEX KEMPER: So, this slide hearkens back to what I was talking about before in terms of the risk of mortality and how it's altered by enzyme replacement therapy. So, you can see that in those individuals who receive enzyme replacement therapy, the risk of death over time is lower.

Again, this doesn't specifically get to the benefits of pre-symptomatic therapy, but again underscores the benefits of enzyme replacement

therapy for individuals with MPS II.

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ALEX KEMPER: So now I'm going to dig into some studies that can help us. And some of the key findings come from these reports of siblings with MPS II.

And the first one that I want to highlight is this study. It's a three-year follow-up with twins, one of whom had MPS II and was treated pre-symptomatically. The other twin did not have MPS II and went right to identification as if there was an older sibling. It was actually a girl who had MPS II leading to the early identification of one of the two twins. I hope that makes sense.

For the twin who had MPS II, enzyme replacement therapy was done at three months of age. By the time of the follow-up, there was basically normal range of movement for most of the joints. There were normal cardiac valves. There was normal facial appearance. The IQs were

similar, 98 for the individual with MPS II, 118 with his twin, you know, with those fine IQ's. The twin with MPS II had mild deformity of one vertebra.

And then the older sister, the one who was the index case that led to the identification in these twins, at age 7.5 has a reported IQ of 24, which had decreased over the three years, and a wide variety of other findings consistent with MPS II.

So, you can begin to see how this can be an insight into the effectiveness of early intervention. But again, it's essentially a case report.

Next slide.

(Slide)

ALEX KEMPER: So, we did find an abstract that actually followed these twins out to nine years of age. And still at the time, no evidence of MPS II in the affected individual who was receiving enzyme replacement therapy. There was reported minor restriction of movement at the hip.

And the IQ has essentially remained stable from before.

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(Slide).

ALEX KEMPER: I want to dive into another study that recently came out, which is evaluation of the long-term treatment effects of IV enzyme replacement therapy using statistical modeling. And as these things, typically happen, this paper came out a few days before our slides were due for this presentation. So, we did plan to follow up with the investigator to get some clarity on the particular study.

But again, this is an analysis from Hunter Outcomes Study. It included males with MPS II who had received enzyme replacement therapy for five years or more. There had to be data from at least two time points, including one after enzyme replacement therapy started. And these individuals hadn't received hematopoietic stem cell transplants or any researched therapy for the MPS II.

They categorized individuals by the age at which enzyme replacement therapy began to under 18 months, between 18 months up to five years, and then five or more years. And then they looked out from eight years.

And they had a wide variety of outcome measures: urine GAG levels; left ventricular mass index; whether or not the liver was palpable; FVC and FEV_1, these are pulmonary function measures. And for this they included children who were older than five years of age because you have to be a certain age to get a reliable measure of FVC and FEV_1. And there is no recorded cognitive impairment.

Similarly, this study also reported the six-minute walk test for subjects who were at least five years of age and had no cognitive impairment at any time. So again, this is a secondary analysis of the Hunter Outcomes Study, looking at outcomes for individuals who meet these criteria.

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ALEX KEMPER: So, the overall study population if we do 481 subjects with a symptom onset at a median of 1.5 years. And the median age at which enzyme replacement therapy started was five years. And about two-thirds of the subjects were reported by parents to have cognitive impairment at some time. Again, this mirrors what you would expect in terms of the distribution of the attenuated versus severe MPS II.

Next slide.

(Slide)

ALEX KEMPER: So, I want to summarize the things that I found out. I talked about the overall sample side, but not every individual had all of the measures. So, you're going to see that there's a big drop in some of the sample sizes.

So, you might expect the urine GAG levels and whether or not there was any palpable liver decrease over time for all subjects. And it didn't really matter when the enzyme replacement

therapy had begun.

For FVC and FEV_1, the pulmonary function decreased slightly after five years with the age group, without cognitive impairment. Remember those are the only individuals that they put in this particular analysis.

And quoting from the paper, which trends similar across all ages at treatments start. Then they also reported for the left ventricular mass index. According to the paper, it remained stable for up to eight years after enzyme replacement therapy in all age groups, with decreases of about 1 gram per meters squared at eight years after ERT, beginning with baseline across all ages at treatment start.

So again, the left ventricular mass index did not seem to vary based on when enzyme replacement therapy started.

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(Slide).

ALEX KEMPER: But what I really want to do is spend some time digging into the findings

related to the six-minute walk test. And these figures are taken directly from the paper. I do want to take some time just to explain what was in this.

So, first of all, the sample size was just 76 individuals with MPS II who were not reported to have cognitive impairment. The values weren't in terms of how far they could walk in this kind of long test, weren't evaluated until subjects were five years of age if the enzyme replacement began before five years of age. And just trying to standardize when the assessment would begin.

And the study provides point estimates for the mean walking distance at eight years after enzyme replacement therapy start. And that was greater for patients 1 year to 18 months after the enzyme replacement therapy was begun, with substantial overlap between the confidence intervals.

So again, I appreciate that what I said was just confusing. So, what I want to do is have

everyone take a look at the figure. First of all, do you see in the light gray in the background? Those are the actual points from the individuals over time.

You can see that they're a little bit messy. And part of this is because these were not prospective data that were collected at fixed intervals for particular subjects at certain ages. Instead, they were just using the data that they had.

The red is for individuals who began enzyme replacement therapy between 0 and 18 months. The blue line is between 18 and up to 5 years. And the black line is when enzyme replacement therapy started after five years. And then these sampled lines, which I would encourage you, you can sort of block them out as you look at these lines, represent the confidence intervals.

I guess the only reason that we would pay attention to these confidence intervals is just showing that there is substantial overlap, which one would expect because of the small sample size.

But if you look out to eight years after enzyme replacement therapy started, even with this -- and sort of putting aside the overlap, individuals who began at 0 to 18 months had a 12.6-meter further walk test than those who began 18 months up to 5 years. And they had a pretty frequent 1-meter further six-month walk test than those who began enzyme replacement therapy after five years of age.

So again, substantial overlap in the confidence intervals, but the individuals who began enzyme replacement therapy between 0 and 18 months did have greater distance on the six-minute walk test.

Next slide, please.

(Slide)

ALEX KEMPER: It's important that we really keep these findings in perspective, given the limitations. So first of all, this doesn't show the statistically significant difference by the age at enzyme replacement therapy. Everyone just saw the wide confidence intervals.

And again, given the sample size and the fact that the data were collected not prospective, but as secondary analysis of the data set, there's really limited ability to conduct statistical inference testing, and those are standardized things across.

I talked about the variability in timing and the number of measures per subject. There's lots of incomplete data. There's a risk of confounding.

The other thing, and this is one of the things that we need to follow up with the investigators, is that in the report they describe this as a pseudo-process general analysis. So, what do I mean by that?

They were looking at each time point individually, not taking into account the trends that might have been happening at the individual level in terms of both falling or increasing six-minute walk tests. So, it's just really looking at each time point on its own.

The other thing, and I should have

pointed this out on the previous slide. Actually, maybe we can just go back. I think it's easier to point this out.

(Slide)

ALEX KEMPER: It is that the X axis is not the age of the child, but it's the time from enzyme replacement therapy start. So, individuals who started at a younger age are younger than individuals who started at an older age on this kind of thing here. So again, that's not the age of the child, but it's the time that enzyme replacement therapy starts.

Okay. Now you can go back again.

(Slide)

ALEX KEMPER: Sorry to make people dizzy by jumping around like that.

So again, the outcomes, like I just said, were based on the times since enzyme replacement therapy initiation, not absolute age.

And then finally, there no information in the study about what led to the diagnosis. And that could have important impact on the degree of

involvement at that time of the enzyme replacement therapy was started.

So, this is an important study, but there are a lot of limitations. It needs to be understood in the context of the available data.

So, I don't want to minimize the importance of having registries and doing these kinds of analyses. But the findings have to be interpreted with some degree of caution.

Next slide.

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ALEX KEMPER: So, let's go back again to the gray literature. So again, I'm wanting to point out three siblings who were diagnosed with different agents six years, two-and-a-half years, and then prenatally. In this report, the age of treatment was a little bit unclear in that the six-year-old's enzyme replacement therapy was listed for four years, not at three years of age, whereas the other ones had enzyme replacement therapy between two-and-a-half years and four months.

You can see their ages right on the bottom. And again, you can see differences in outcomes. But again, the ages are all different. So, it makes predictions for the youngest one and where these can end up a little bit challenging.

But again, I really think that it's these kinds of studies that can give the most insight into the impact of pre-symptomatic enzyme replacement therapy.

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(Slide)

ALEX KEMPER: So, let's move back again and talk about some of the laboratory stuff. As I mentioned before, measuring GAGs are the way to rule out pseudodeficiency.

But Michael Gelb at the University of Washington shared with us a report that's been submitted for peer review that, without taking names of the specific laboratory issues, it does seem that the GAG markers are a valid and reliable way to ensure -- or to separate out pseudodeficiency versus MPS II.

Next slide.

(Slide)

ALEX KEMPER: One of the things we haven't talked about and we're looking at the gray literature for our novel therapies, including -- it's always hard when you have these like new therapy drug names that I don't want to slaughter.

So, I'm just going to say for the first bullet point that it's an enzyme replacement therapy that uses a transparent receptor to cross the blood-brain barrier that's been approved in Japan, with trials that are ongoing in the United States.

There's another similar product that has clinical trials just underway, and it has been granted FDA fast-track designation, which means it will be sped through the review process once the data are available.

And then the last one here is a gene therapy that's just now beginning investigation. It's going to be delivered directly into the cisterns. And there's also work that's going on

around intrathecal idursulfase.

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(Slide)

ALEX KEMPER: Let's go back again and talk about what we've learned from the newborn screening programs. We talked a little bit about Illinois. What I can tell you is that from December 2017 through May of 2021, they screened about 475,000 newborns, with 63 who screened positive. And you can see a breakdown there in terms of severe, affected, and variants of unknown significance.

One of the challenges in terms of interpreting the data that's collected with the newborn screening program is that sometimes LIMS system classifies -- the way they record a classification isn't the ones that we typically use around the conditions. Some of that has to do with, you know, how the LIMS systems are updated and that kind of thing.

This is why you see the term here, "classical," which is not something that is

typically used when talking about MPS II. You can see that they have identified 30 pseudodeficiency, 9 normals, 1 lost to follow-up, 1 parent who refused further testing, and then another 6 who are in the process of being evaluated.

Next slide.

(Slide)

ALEX KEMPER: In terms of Missouri's trending data from November 2018 through June of 2021, where they screened just about 200,000 newborns with 28 screen positives. Three of them were severe. Nine variants of unknown significance.

Again, I thought these were about how it was going to be challenging to figure out if an individual is going to turn out to have severe or attenuated or neuronopathic or non-neuronopathic disorder.

Three cases of pseudodeficiency, seven normals, one lost to follow-up, one refusing testing, and four who are still in the process of being evaluated.

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(Slide)

ALEX KEMPER: So, in terms of the screening results, the first I had been referral rates to the numbers that you could on to get by massive testing. You can see it's between 13 and 14 per 100,000 births. And then in terms of cases identified, 1.7 to 1.5 per 100,000 live births, which again is what you would expect based on our knowledge of the epidemiology going into this review.

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(Slide)

ALEX KEMPER: So, I am going to switch gears a little bit and bring in Dr. Prosser -- hopefully, she can come in and be promoted to presenter -- to talk about how we use the findings that I've shared with you before to do the kind of population modeling that is a component of our evidence review.

So, Lisa, are you there?

LISA PROSSER: I am here. Can you see

and hear me?

ALEX KEMPER: Excellent! It's a technology miracle. We can see and hear you.

So why don't you go ahead? And then once you're done, I'll take over again.

LISA PROSSER: Terrific. Thanks so much, Alex. Good morning, everyone. Thanks for the opportunity to share a little bit more information about the decision-analytic modeling that we're using in the evaluation of MPS II.

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LISA PROSSER: So, is there a question? Georgianne has her hand raised.

GEORGIANNA ARNOLD: Well, yes, but I don't mean to interrupt now. I can wait till the end.

CYNTHIA POWELL: Okay. Yes, we'll wait. Thank you.

LISA PROSSER: Okay, great. Thanks. Just wanted to check on that. Okay, thank you.

So, as this slide shows, as its previous

conditions we will be planning to do simulation modeling to estimate population health outcomes for newborn screening compared to clinical detection.

So, this slide depicts a schematic of the model. In this model we will be simulating a cohort of hypothetical newborns for who are not at otherwise higher risk for MPS II, comparing newborn screening to clinical detection.

In the newborn screening arm, the model, as you can see, each arrow here represents the probability. So, under newborn screening, there is each newborn who undergoes screening will have some chance of experiencing a positive screen or a negative screen. For those who screen positive following confirmatory testing, they will be categorized as confirmed probable, or pseudodeficiency.

Again, keep in mind that the timeframe of this model, it's not all happening instantaneously and that for those with confirmed MPS II it may take some time before they are then further

classified as attenuated or severe.

However, from information that we have from the pilot newborn screening programs, as well as from the literature, we'll be able to create some probabilities and ranges to estimate the proportion of newborns who are likely to fall into each of those categories.

Again, under the clinical detection arm of the model, again we'll be projecting what the comparison would be of the numbers of newborns, from this case individuals, who would likely be detected, again within a newborn growth cohort of roughly 4 million, what the likelihood of having attenuators that we are given diagnosed with MPS II.

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(Slide)

LISA PROSSER: So, the goal here is to provide for the Committee some context on what the projected number of screening outcomes in cases identified would be. As in previous analyses, our goal here, again given the scarcity of the data

typically available for newborn screening, their goal is there is to provide ranges of the screening outcomes.

So estimated range of positive screens that would likely be anticipated if newborn screening were to be implemented at the national level, as well as again the estimates of the numbers of identified individuals within MPS II.

And then further categorized by attenuated, severe, and then another category of probable MPS II for individuals who will be identified and potentially diagnosed during the screening process but may not exhibit symptoms for a longer period of time.

Different from other conditions that we have previously modeled, the evidence review group has made the determination that for MPS II there is insufficient evidence to model longer-term outcomes. In previous conditions, we have typically used either mortality or a number of outcomes we've had, other markers of disease progression that we've been able to project the

number of cases that would likely experience those outcomes with or without newborn screening.

But here, as Alex has just given an in-depth overview of the evidence involved, there is evidence of the effectiveness of treatment. There is at this time insufficient evidence to model the attributable incremental effectiveness that would be associated with earlier detection, diagnosis, and treatment.

This is due to a number of reasons, listed here on this slide, including the heterogeneity of outcome measures, the continuous progression of disease again, and most of the conditions that we have used simulation modelling to protect population health outcomes. We are typically looking at conditions which result in early mortalities, so within the early childhood years.

And here again, it is challenging to conduct modeling, given the very wide range and different types of systems that may be impacted in terms of profiles of these progressions.

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LISA PROSSER: So, in lieu of being able to provide those population-level outcomes for markers, or for health outcomes associated with longer-term MPS II, the evidence review group will be conducting, or our decision analytic modeling team will be conducting an additional systematic review of the health outcomes that have been included in the clinical trials to identify and to be able to provide additional information to the Committee and future researchers to guide additional studies in future understanding of the effectiveness and potential effectiveness of earlier diagnosis and treatment of MPS II.

So, we'll be doing a systematic review to understand both the range of outcome measures that have been used in clinical trials, and this is a BRT, as well as to be able to characterize part of the most common measures. And then again, bringing this back for a technical expert panel to be able to write guidance to the research

community about where to focus efforts.

I will also provide information on review study designs from the previous condition reviews, as Alex has already included, some of the evidence that we have used for previous decision-analytic models that relates to sibling studies or other studies which have really been able to characterize, in a sense, a cohort that in many ways can proxy for a newborn screening cohort, which then provided the ability for us to make inferences about the effectiveness of earlier diagnosis and intervention.

Listed on the slide here, we would also look to be able to provide some evidence for potential study designs. We've seen one very recent study that's been released from data using the health outcomes study, and we believe that there are additional potential uses of those data that might be able to provide some additional evidence there.

So, I'll pause there and turn it back over to you, Alex.

ALEX KEMPER: Great. Thank you. Thank you very much for that overview.

Next slide, please.

(Slide)

ALEX KEMPER: So I just want to update everyone with the status of the Public Health System Impact Survey, which has been fielded from September 20th through the end of October. I know that there are some 40-plus newborn screening programs that that have filled in those surveys. So if you represent one of those programs, thank you very much.

APHL has also been meeting newborn screening program interviews. Illinois and Missouri have been completed. We have one pending with New York. And then we're also in -- and when I say "we," again it's APHL that's leading this. It was Elizabeth Jones and Jelili Ojodu also interviewing other states that might be doing a pilot study or that aren't considering MPS II right now, just understand what kind of issue might arise regarding adding MPS II to newborn

screening.

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ALEX KEMPER: We've also been working on the cost assessment, and I'd like to thank Dr. Scott Grosse for his work on collecting and interpreting those data. As is typical, we consdier both the start-up costs for adopting MPS II newborn screening, as well as the operating costs in the newborn screening program.

Laboratory, clearly the costs faced by the newborn screening program for screening for MPS II is going to vary based on unique characteristics of the program and the way that the screening is going to happen, as well as the number of births within the state.

As we've talked about when we reviewed our methods before, really putting ranges around what these estimated costs are, given there are some new variables that go into things. And so far we have the estimated range for newborn screening for MPS II of between one and six

dollars.

Next slide, please.

(Slide)

ALEX KEMPER: So, in terms of next steps, we're completing the evidence synthesis. As we've done in the past, we're going to close our literature search 30 days before the report deadline in February. I guess it's really the end of the January that the report is due.

The real focus of our work right now is on trying to figure out more information about the treatment impact related to earlier identification that might happen through newborn screening. I suspect that this is going to be a key consideration. It's always been a key consideration for the Advisory Committee.

There is another abstract that we didn't present. It's been submitted to a national meeting that has sibling data. But per our rules, we have to wait until that abstract has gone through peer review. So hopefully that will be done soon and we can talk about that some more in

the February meeting.

But again, this abstract describing siblings is really sort of along the lines of what I presented earlier.

Dr. Prosser talked about the modelling screening outcomes based on available evidence, really focusing on the number of newborns who would be detected through newborn screening versus usual clinical care. And also outlining opportunities for investigators in the field about the kind of data that need to be collected to be able to do more specific population health modelling. And then finally, working with APHL. And Dr. Scott Grosse is completing the PHSI assessment and cost evaluation.

In terms of where we are with our timeline, we're doing very nicely. And I don't anticipate any problems with having these final pieces completed well in advance of the February meeting, when that occurs.

Next slide.

(Slide)

ALEX KEMPER: And with that, I'll open things to questions.

CYNTHIA POWELL: Thank you, Dr. Prosser and Dr. Kemper, for this mid-term review for MPS II.

And now we'll open it up for questions and discussion. We'll have the Committee Members discuss first, and then organizational representatives will follow.

As a reminder, please use the raise-hand feature in Zoom when you would like to make comments or ask questions. When speaking, please remember to unmute yourself and state your first and last names each time you ask a question or provide comments to ensure proper recording for the minutes.

QUESTION AND COMMENT PERIOD

CYNTHIA POWELL: Okay. First I see Committee Member Scott Shone.

SCOTT SHONE: Yes, Scott Shone, Committee Member.

So, Alex, you know, the prevailing theme

that I pulled and what helped me understand, if I should, is there appears to be just a paucity of data, particularly quantative data, around.

And I don't want to misquote Lisa. I tried to look at the transcript while she was speaking so I could write it down. But she said something to the effect of, she said, "As Alex said, there's insufficient evidence," and then she went on to say, "to model the effectiveness of treatment attributable to early detection and intervention." Something to that effect. Please correct me if I'm wrong.

So two quick questions, if you'll indulge me. The first is, am I right in assuming there is a paucity of data? And if so, is that because of the ultra-rarity of this condition? Or that there isn't much in the literature around the outcomes that can be drawn to extrapolate what we need for early intervention if there were screening?

ALEX KEMPER: Yeah. So that's a great question, one that we struggle with. And I'm glad you're giving me the opportunity to amplify my

comments from before.

So this is what we know. We know that enzyme replacement therapy is effective. There's no question about that. And at least for the older children, it does seem that earlier intervention, sort of after when they would become clinically defective, there just seemed to be a benefit there.

The real question that's challenging is, because treatment that's initiated because of newborn screening, so you know, early infancy, leads to better outcomes. And it's difficult to get there because, first of all, there's limited experience in screening for MPS II. So it's not like there are large sample sizes of children who were identified through newborn screening.

So when that happens, we oftentimes have to rely on these case series and that kind of thing which I presented before. So case series really can't be used in the quantitative model that Lisa and her team does. It's just, you know, you just can't assign probability when you're

dealing with siblings and those kinds of things.

So I don't want to say that there's no evidence at all about the effectiveness of early intervention. But we simply don't have the kind of quantitative data that it would be nice to present to you.

We're in this unique position of having the Hunter Outcomes Survey. So kudos to everybody who's involved with that for setting for setting up a registry to correct the information. But it's just the nature of the condition that there are not going to be a lot of children who were treated pre-symptomatically in that registry just by the nature of the condition.

So what I don't want to say is that insufficient data for the modeling means there is insufficient evidence to make a recommendation. But I think you all as Committee Members are just going to have to decide where you put the weight on these sibling case series and that kind of thing.

And I think that -- this is why it's

challenging to be making a recommendation -- that there are other bits of evidence that you can use to infer that, you know, like that other study from the Hunter Outcomes Survey that I carefully walked through before, to the degree that we use and interpret that to reflect early intervention.

Again, these are all very difficult things. But just the rarity of the condition and the fact that there hasn't been a large number of individuals who have gotten treated based on newborn screening is really what makes this gap challenging.

Does that answer your question?

SCOTT SHONE: It does. And I'm glad you brought up the six-minute walk test because that was the second question I had. I'm really struggling with how to -- you spent a lot of time on that. So, you know, I really want to pay attention to that because I feel that, to me, that indicates you think there's value there if you spent all that time really clarifying the outcome of that and making sure that we understand that.

I'm really struggling, Alex, with extrapolating that to, what is the weight of that? What does 33 metres more in six minutes mean? Like how can we understand what that means? How does that translate to a sort of demonstrable evidence of beneficial outcomes?

And related to that on your next slide, you said in the gray literature there is significantly slower disease progerssion, which again is a qualitative assessment.

If you really come from a quantitive, a 33-meter, help me to understand how that relates in your mind and how should we as a Committee think about that? After your presentation and reading through your slides, I'm kind of struggling with lesson 8 from this.

ALEX KEMPER: Yeah. That paper came out, I think it was October 30th when the paper was published and came out. So I really do want to talk to the investigators and there just wasn't time with when everything is due to be able to do this because of the other limitations that I

described around there.

And what I can't tell is when there are these between 10- and 30-meter differences, you know, just getting rid of the confidence interval set of things, but just like you need to point out problems.

What I can't give you is, say, what does this mean to the families? You know, how does that improve the quality of life? And then the other thing, because they're at measure, you know, let's just say there's a 30-meter difference in this six-minute walk test. What I can't tell you is what happened over time. Is it sustained? Does the difference diverge? We just don't have that information.

So I hate not to provide a direct answer for you. But the impact of that 30 meters, I think that that is a question not that we can't answer, but that's one for families.

All right, Lisa. You talked so much this modeling and all. I don't know if you want to add anything to what I just said.

LISA PROSSER: Yeah, I just want to highlight either that there is a difference between what conclusions can be drawn from the evidence about the effectiveness of treatment, and then doing what we're specifically referencing with respect to the modeling, is that, because of course it is clearly evidence, the sibling case series that are available, the evidence of treatment.

But where the evidence is insufficient is to make that next step, to quantitatively characterize what the incremental, attributable benefit of correllary diagnosis and treatment would be at the population level. So I just wanted to highlight that one thing.

ALEX KEMPER: Can I add one other thing on, which I should have added before? Well, we know from sources that the enzyme replacement therapy has limited effect on CNS disease and those outcomes. And again, that six-minute walk test is restricted to the individuals whose parents reported that they didn't have cognitive

impairment as well.

So again, when we just focus on enzyme replacement therapy and its effects based on that study, again it's just one more caveat in terms of interpreting it.

CYNTHIA POWELL: Okay. Shawn McCandless.

SHAWN McCANDLESS: Thanks. This is Shawn McCandless. I'm a Committee Member.

Hopefully this will be a slightly easier question to answer. In the Illinois data that were presented, there were eight patients that were reported as variants of unknown significance. And I'm just wondering, what does that mean in this context of newborn screening? And what happened to those individuals?

And then for Dr. Prosser the question is, How do you know that in your model? Where do you put them in your model? And secondly, do you have a mechanism for identifying adverse or negative effects being considered a variant of unknown significance?

ALEX KEMPER: So first I want to thank

Shawn for all of the work he's done as a liaison and pushing us to think about these issues. And again I'm going to give you a very long-worded answers to what might otherwise be considered an easy question.

So the challenge in looking at outcomes from newborn screening, this has come up in other conditions, is that the laboratory perspective and then there's the follow-up program perspective. So when we talked about the variants of significance, part of it is that sort of putting it into the laboratory information management system that's been developed for other conditions. And so it doesn't fit entirely with that.

So we did have a separate call with the individual who was responsible for follow-up. And what I can tell you is it's still a work in progress, classifying exactly where those children are going to fall into.

So it's difficult to figure out if the individuals are going to be attenuated or severely infected because, you know, we need time for

things to declare themselves if it's not clear from the genotype.

And what I can tell you is that the follow-up program, because the individuals in the follow-up programs to themselves are not responsible for doing that management, is they're still trying to gather that information.

So I would say the variants of certain significances is probably not the way that we all from a health policy standpoint or evaluation side of things would like to talk about it. But that's just the way the laboratory system collects the data.

And then the follow-up system is still working with the people who are actually providing the follow-up care to be able to find out what's going on with those individuals.

So that's why the terms are that way. It's 100 percent not clean, but it's just the way that newborn screening programs and follow-up programs work.

SHAWN McCANDLESS: So, this is Shawn

McCandless again.

So in the model, they would fall under probable MPS II?

LISA PROSSER: Yes, that's right. And I should have labeled this as a draft model schematic because this is where we would typically add a number of footnotes and definitions to be really clear about what's being included in each of those categories.

And again, to keep in mind that for the end points of that tree in classifying attenuated and severe, some of that will be projected based on other evidence in the literature and not directly based on outcomes from the laboratories.

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Okay, yes. Mei Baker, Committee Member.

Actually, then you follow up with Shawn's question about the variants of significance. Also there's a probable. So actually, I have a second question, but it's also sufficient as to the situation.

But the additional question I have for Lisa is, you've got a category. You put in your severe, you know, mild. Then this one, probable, you want to define this as a benefit or harm. So that's why kind of I struggle a little bit, because you've used most time when you have variants of no significance, most time, a lot of times it cannot be benign.

So you've got a category in that. To me, the category is a harm. When you said probable, could potentially have disease, I think it's different. That's just my -- so I don't know --

(Crosstalk)

ALEX KEMPER: I'm the person to agree with you. And this is just a vestige of how the laboratory -- their ability to record the information that they have, right? Because variants of uncertain significance often are things we're not sure. And it can grate on the families. You know, the kind of follow-up that they need is complicated versus individuals who might be clear that they have the disease and can

begin to talk about enzyme replacement therapy.

So I 100 percent agree with you. And it's the vestige with the way that the LIMS system is the state works.

MEI BAKER: Okay. My additional is the more for clarification, I believe. In that flowchart Lisa presented, have the false positive and the presence of pseudodeficiency. I'm just wondering, the way you present means you have false positive, also including pseudodeficiency? Or pseudodeficiency is another term you use for your model for false positive?

LISA PROSSER: So right now they are combined. We can separate those out, do whatever is more useful to the Committee. And in the past we have. We have modeled those separately. So it could be done either way.

MEI BAKER: Thank you. I do not know. I don't think about it as useful. I just want to be sure --

(Crosstalk)

LISA PROSSER: Yeah. Yeah. We'll be

really clear.

(Crosstalk)

MEI BAKER: Okay.

LISA PROSSER: Thank you for that feedback. Thank you, Mei.

MEI BAKER: Well, because in terms, the consequence is the same.

LISA PROSSER: Yep.

MEI BAKER: Because we don't want them, right? Okay.

One more for Alex. So you estimated the cost at $1 to $6. So my question is, the range, is it because if we used a laboratory or already have the instruments so that you just need to worry about a reagent and the multiplexing, so you can get a lower end. Is the $6 is the high end? If you don't have anything, do you need to purchase everything?

ALEX KEMPER: Yes. It has to do with the technologies we use and the degree to which you have to purchase reagents. So if you have to adopt, for example, the fluorometry versus

incorporating tamdemmass and that kind of thing.

And again it's difficult to get to costs just because different programs are coming in for things with different resources ahead of time. And so, you know, I don't think we can promote Scott, he could talk about the costs if he wanted.

But I feel most comfortable putting these ranges on it and describing the kinds of things that individual programs have to do as they move forward with it, so that they can understand that. But the range is somewhere between there.

MEI BAKER: Thank you.

CYNTHIA POWELL: Jeff Brosco.

JEFF BROSCO: Jeff Brosco, Committee Member.

I'll start with a comment and then I have a specific question that I think will be easy for you guys. And the comment is related to not just this condition, but a number that are coming through. And that is, figuring out what "benefit" really means. You know, and Scott asked about these 33 meters live, and Alex has said, "Well,

you know, a lot depends on the families."

And I guess we could try to make some sense of that by saying, "Well, what's the mean that you go in six minutes?" Right? And try to figure it quantitatively. But for this condition and many others, there are still going to be some issues even after full treatment. Right? Morbidity continues.

But having some research in this HRSA MCHB, big money comes in, or other organizations. Let's try to get at what really matters to families, per condition. And then making sure that the nominating groups look forward, saying, "These are the outcomes that we think are important." So what's beyond mortality is, someone is able to walk this much further. Someone is able to do these things more.

And there is some research now, of course, in patient-centered outcomes. But I feel like we really need to have a lot more of that to be able to make good decisions in this Committee about whether the investment in newborn screening

is worth the outcome.

I'll probably say that three more times in the next two days because I think it's so important.

(Inaudible interjection)

JEFF BROSCO: All right. Go ahead. Yes, go ahead.

MELISSA PARISI: No, no. Go ahead. Go ahead and then I'll ask.

JEFF BROSCO: All right. So the specific question is, as I was following that, it seems like there are at least five individuals who've been identified in pilot state newborn screening programs. Is it possible to get outcomes on those children to get a sense of what's happening with them? Or are they just so new that we don't really know yet?

ALEX KEMPER: Well, I think that it's so new it's going to be hard to say anything just because it takes time for things to evolve. But we've been in conversation with follow-up folks just to see what it's possible to get. And even,

at what point did they decide to begin, assuming that they did begin enzyme replacement therapy or some other kind of therapy.

But getting back to your philosophical question, one of the things that I learned on the Technical Expert Panel call that I thought was really important was the point around toiletting. And that is, you could have an intervention so that the toileting is easier as the child aged. Because that would make a profound effect on families.

Unfortunately, we haven't been able to find the kinds of data that I was hoping that we would find around that. So I do think that there are these measures that these clinicians don't realize are so important to families. So I think that's such an important point that you've made, Jeff.

The other thing is that I just want to be again very careful about, you know, it's not just 30 meters. Because the population was so restricted in terms of that analysis included.

And I just worry that they're going to call people and say, "Well, there's a 30-meter difference if you begin this enzyme replacement therapy earlier."

But there are a lot of potential issues with this study that may limit what you can read that study as. So I just again want to put a certain caution flag around how much weight to put in 30 meters.

JEFF BROSCO: It's Jeff Brosco again.

I want to clarify because I remember the nominating group where you had concerns that early treatment may not affect cognitive ability. And then although there might be some improvements in some organ function, which is really important, it may not be in terms of cognitive ability.

And so to your point, figuring out what's really important to families -- toileting might be so important it's worth it for newborn screening.

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Thank you. And I just wanted to thank you. This is Melissa Parisi from

NIH. And thanks for that presentation.

I wanted to make a comment for the evidence review group that the NIH is actually funding a pilot screening project through RTI in conjunction with the State of North Carolina for MPS II.

That was just awarded in September, however, so I don't think that they will have much data available for your review in time for final presentation in February. But just wanted to let you all know that there is another pilot project that is ongoing for MPS II.

ALEX KEMPER: That's really helpful. I didn't realize that. So we should reach out to them, and especially because that can inform us around certainly the implementation side of things, even if they haven't gotten to actual screening.

MELISSA PARISI: Okay. Thank you.

CYNTHIA POWELL: Mei Baker, did you have another question? Or still had your hand up?

MEI BAKER: Sorry, I forgot.

CYNTHIA POWELL: Okay. That's all right, no problem.

Before we go on to our organizational representatives and their questions, I had a couple of things. This is Cynthia Powell, Committee Member.

I do think that it's helpful to separate out the pseudo-deficiencies from the other false positive cases. I don't know that data for MPS II, but I know for MPS I, certain ethnic groups do have a very high frequency of pseudodeficiency allelles. And you know, it may sort of falsely look like it may be an issue with the screening test itself versus just the high number of pseudo-deficiencies in that particular state.

The other thing -- I'm sorry if it's too granular. But, Alex, the Tilke (ph) article -- I'm not too sure how you pronounce the author's name, but that paper about the two twins, one affected, one not. And they were treated; one of them was treated early. And then they had the older sister with severe MPS II.

I was just wondering, did the authors provide any reason for why a female would have such a severe case?

ALEX KEMPER: No, it was just fragmented. What I can say is that I read the paper a few times, because I was like -- at first I thought I had misread it that there was an affected female. But the paper said it. That's all I know.

CYNTHIA POWELL: Okay. Thank you.

All right. Let's see. Going on, I think Georgianne Arnold had her hand raised for a long time. So we'll start with Georgianne.

GEORGIANNE ARNOLD: Well, thank you.

I have to say Shawn asked most of my questions. But one of the things that I think is not clear to me is, when states declare their effective rates, what are they using? Are they using the cases that are proven? Or what are they doing with the mousess?

Are GAGs, urine GAGs is really enough to tell affected from unaffected. And I think that that is missing kind of not only from this

literature, but from most of it with this newborn screening of how big of a problem is the -- we don't know.

And I would like to see states address that in their data. And I began looking for where that was put in the model, but I think Shawn asked that question.

ALEX KEMPER: Yeah. The only thing I can comment on that is the work that Dr. Gelb has shared with me, and then that new descriptive list was submitted was that they took dried blood spots from affected individuals, pseudo-deficiencies and unaffected individuals and were able to show that measuring the GAGs clearly separated out affected from unaffected people, or individuals.

So I think that in terms of the diagnosis, I think that the bearings of uncertain significant issues marked just like I said an issue to related to how the LIMS system is lacking information on those people.

But I'm not a laboratory person. So I always feel nervous when I say this. But it looks

like the data are pretty compelling that measuring GAGs can separate out pseudodeficiency from those without.

CYNTHIA POWELL: Natasha Bonhomme.

NATASHA BONHOMME: Thank you. Natasha Bonhomme, organizational rep.

A question and a comment. My question is, in the data that you were able to look at, was there any indication regarding race stratification of the screened positives and particularly those pseudo-deficiencies?

I know we were talking about separating out those pseudo-deficiencies, but really trying to get a sense of, you know, is it a test issue or is it the fact that who we've seen in clinic has maybe come from one type population, and as we go into a really population-based screening, we need to be looking at that.

So just if there's any data that look at that.

ALEX KEMPER: That's a great question. And I actually don't remember looking at that.

And I think that's an important issue, too, in terms of equity in the future that the data that we have are going to reflect the population, you know, all children at once. You know, if they were to get screened.

And I kind of think we have to go back and look at that. I just can't remember looking at that in particular. So we should.

NATASHA BONHOMME: Great. Yeah. I think that would be really important. Especially as the discussion of newborn screening and equity takes up more and more space, as it should, that will be really key to that.

And then my only comment is really, it's just kind is for observation. I think it's really interesting when you were talking about the language used in and follow-up -- I don't like to say versus lab, because it's all part of a system.

And just really thinking about that and maybe as more of a 30,000-foot view of if there are ways that we can bring some harmony to, you know, what we're talking about, the indicators in

the data, that's like if you're lab, and what we need to know from the follow-up side to actually know how this is impacting families and more of those long-term outcomes. So just a comment on that.

ALEX KEMPER: No, thank you. No, this is an issue that comes up all the time. So I'm glad you raised that.

CYNTHIA POWELL: Debra Freedenberg.

DEBRA FREEDENBERG: So both Shawn and Georgianne addressed most of my questions, but I just wanted to clarify a few things.

One is that, going back to those variants of uncertain significance, those individuals did have GAGs detected as well, which is why they were not satisfied as to the deficiency?

ALEX KEMPER: Yeah.

DEBRA FREEDENBERG: And the question within that was, then the severity, whether it was an attenuated or a severe form, which we often face in lots of different positions. And I just wanted to make certain I understood that properly.

ALEX KEMPER: Yeah. And they're still being worked out.

DEBRA FREEDENBERG: Right.

ALEX KEMPER: In terms of, you know, talking to the follow-up, we haven't been able to get the information in terms of where they're expected to fall. And like I said, you know, it can take a while to figure out if they're being attenuated or severe.

But it is difficult to get this information. And I think it gets back to what Natasha was talking about in terms of unifying their data-collection systems.

DEBRA FREEDENBERG: Then the other comment I wanted to make was related to the question about the six-minute walk test. That particular measure has been an assessment that's been around for quite a while. And it is what was utilized to justify the approval of the enzyme-replacement therapy. I remember the -- diseases. That was one of the things the FDA looked at when the ERT's were approved.

I can't comment on the significance for families. But that has been like the traditional measure that's been out there for years, just to kind of put it in perspective as well.

And then the third thing that I wanted to comment on also is, it's not just lab and follow-up terminology. There's also the clinical terminology that needs to be integrated back into the whole system, because there's very different terminology utilized.

ALEX KEMPER: Hundred percent agree.

CYNTHIA POWELL: JEd Miller.

Jed MILLER: Yes, hi. Jed Miller, Association of Maternal and Child Health Programs.

Two questions. First one I think it was kind of answered in your response, Alex, to Dr. Powell's question about the sister who appeared to be impacted with the two younger twin brothers, was about comparability of her clinical picture and everything. I imagine that there is not much known on that. I just wanted to ask.

ALEX KEMPER: Correct. Yeah.

Jed MILLER: Okay. Thank you.

And then the other question is about the survival table for the 100-outcome survey about percent with cognitive impairment. Do you have a comment on the methodology for that, for engaging cognitive impairment? Was it a binary question? Were parents given the opportunity to go with and talk about severity? And have there been any analyses within that realm about if it's not binary?

ALEX KEMPER: Yeah. I can't comment on all the different ways that cognitive impairment might be captured in the Hunter Outcomes Study. What I can tell you is in the study that I showed with the six-minute walk test, it was just dichotomized based on what the parents said.

And so for that curve that showed the enzyme replacement therapy and the separation, I'm not sure if they used anything more granular than that, you know, parent-reported dichotymous outcome.

CYNTHIA POWELL: All right. Any other

questions from Committee Members or organizational reps?

(No audible response)

CYNTHIA POWELL: Once again I'd like to thank Dr. Kemper and Dr. Prosser for their presentations today. Thank you to the Committee Members and organizational reps for your questions and comments. And we look forward to the final ERG report in February at our next meeting.

ALEX KEMPER: Thank you.

OVERVIEW OF IMMEDIATELY ACTIONABLE COMMITTEE PROCESS UPDATES

CYNTHIA POWELL: All right. Next I'd like to go on to Overview of Immediately Actionable Committee Process Updates, if I could have those slides brought up.

While we're doing that, in February of 2019, the Committee convened an Expert Advisory Panel to review Committee processes for nomination, evidence-based review, and decision-making; and identified processes that could be updated in order to strengthen the nomination,

evidence-based review, and decision-making processes.

Throughout the review process, the Committee has discussed the proposed updates and received public comments. At the Committee's last meeting in August, Dr. Kemper and I presented an overview of areas under consideration for potential update which were categorized as immediately actionable, or requiring further discussion, research, or policy change.

Today the Committee will vote on the items identified as immediately actionable. I'd like to emphasize that throughout the review process, there were many recommendations identified that merit further consideration, and we will continue to explore feasible next steps.

In preparation for today's vote, I want to briefly review the immediately actionable updates that we intend to vote on today. And we'll vote on those as a complete package.

Committee members, in the briefing book, in addition to this presentation, you received an

overview of the items up for vote; the review of the Advisory Committee on Heritable Disorders in Newborns' nomination; Evidence-based Review and Decision-making Process final report, which provides a detailed explanation and rationale for each of the proposed updates; the updated nomination form; and the draft decision matrix guidance, all of which will be referenced in the next several slides.

So the main focus areas are the nomination; the nomination form and process; the evidence-based review; assessing published and unpublished evidence; assessing public health system impact; and assessing stakeholder values, the decision matrix, and review of conditions on the RUSP.

Next slide.

(Slide)

CYNTHIA POWELL: For the proposed next steps categorized by level of actionability, these were separated into those immediately actionable, needs more discussion, needs more research, and

needs policy change. And right now we're focusing on the immediately actionable.

Next slide.

(Slide)

CYNTHIA POWELL: So, concerning the nomination process, the issue is that information requested from the nomination form does not directly link to specific and relevant information needed for the evidence review in areas such as registries, unpublished evidence, the screening algorithm and resources, and long-term follow-up, among other things.

Revisions have been proposed for the nomination form. The new nomination form will be posted on the Committee website in fiscal year 2022.

Next slide.

(Slide)

CYNTHIA POWELL: For the nomination form, highlighted in green are those new additions proposed, including the enzyme if there is one.

For incidence, include the U.S. Incidence

Estimate and Citation.

For the timing of clinical evidence, the relevance of timing of newborn screening to onset of clinical manifestations, for the phenotypes that would be detected with screening.

For the Severity of Disease, include the U.S. distribution and the prevalence of known phenotypes, if applicable.

Next slide.

(Slide)

CYNTHIA POWELL: And regarding treatment, in the Modality of Treatment, to describe the medical and clinical care required, whether that be drugs, diet, replacement therapy, transplant, or others; and identify which treatments are current standard of care.

For clinical indications for treatment, what are the clinical indications? Including the ages of treatment initiation, clinical symptoms or severity, among other indications. For the current standard of treatment -- identified above.

What are the contra-indications for

treatment initiation? Regarding availability of treatment: Are treatment and follow-up available in most hospitals, major medical centers? And describe the follow-up and specialized treatment centers which may be needed.

Next slide.

(Slide)

CYNTHIA POWELL: Continuing with suggested changes for the nomination form, regarding the validation of the laboratory test for the specimen sample. If it's not the dried blood spot that's being used, indicate any timing requirements in screening or specimen collection that would be needed.

Regarding the screening test, the platform and procedures, include the number of samples run in high throughput, the instrumentation, whether tandem mass spec or digital microfluidics or others, and if available, as part of a multi-analyte platform.

For disposables, the lab-base analysis or off-the-shelf kits, which ones are being used? If

off-the-shelf kits, have these been FDA approved, and what are the vendors or suppliers, if known? And for the modality of specimen sample for tier 2 test, what type of method would that be? And also regarding the screening test.

Next slide.

(Slide)

CYNTHIA POWELL: For analytical validation, and we had one suggested insertion of a word with this one. Has the CDC's Newborn Screening and Molecular Biology Branch been contacted regarding these and our other validation measures currently pending or available?

And then for the timeliness, does the condition qualify as time-critical from a timeliness perspective, requiring immediate medical attention? Regarding incidental findings, would there be an addition to secondary findings, also incidental findings that would be discovered in screening?

Next slide.

(Slide)

CYNTHIA POWELL: For confirmatory testing methods, include samples/specimens needed, whether it be blood, radiology tests, urine, tissue sample, biophysical tests. And if available, to include the sensitivity and specificity for clinical and analytical validation.

Regarding regulatory status of confirmatory testing, is the test FDA cleared or approved? If so, include the year and the reference. Describe availability of confirmatory testing, information, sole source manufacturer, specialized testing centers, et cetera.

Regarding short-term follow-up and diagnosis, how is the diagnosis confirmed, whether it's by laboratory or genetic testing, clinical evaluation, symptom onset, or other? When is the diagnosis confirmed, such as time to diagnosis by phenotype?

And who can diagnose newborns with positive screens? Would this be a primary care provider, specialist, major medical special centers, et cetera?

Next slide.

(Slide)

CYNTHIA POWELL: Regarding any pilot studies that have been done, provide information regarding those pilot studies, whether done in the U.S. or international. And if in the U.S., which sites, cities, or regions?

In terms of screening methods and algorithms used, describe the screening method and algorithm. Attach a flowchart with pilot outcomes. Include confimatory testing methods, again whether genetic or other types of confirmatory testing have been done.

And in terms of the number of infants confirmed with the diagnosis, include the number of infants identified as having a positive screen and referred for confirmatory testing. Of those referred, the number of infants confirmed with a diagnosis, time to abnormal newborn screening and result obtained, time to diagnosis confirmed, and time to treatment initiation.

For key outcomes of treatment, what are

the key outcomes of interest? For which of these key outcomes is evidence available, and what is the follow-up period? What plans are there for longer-term follow-up of newborns detected early in these studies with ongoing studies, clinician follow-up, or other?

Population-based screening contacts. Cite reference if available and/or program contacts to follow up with about programs conducting prospective population-based screening, whether it be pilots or others.

Next slide.

(Slide)

CYNTHIA POWELL: For pilot studies or states that are already screening, include which states are currently screening for the condition, states that are currently mandated to screen for the condition, and states considering screening but not mandated.

And with patient registries or databases, list registries or databases curently established for the condition. Are there unpublished data

that would inform newborn screening? If yes, who holds these data?

Next slide.

(Slide)

And finally, there's currently a limitation on the number of references, but the recommendation is that there be no lmit on the number of references that can be included.

All right. So I'd like to open this up for discussion now. Again we'll have Committee Members go first, followed by organizational representatives. And please state your name and affiliation before speaking.

Mei Baker.

MEI BAKER: Mei Baker, Committee Member.

I have a quick question. For the first page, you have adding on the enzyme. I was wondering, some disorders actually it's not enzyme problem. Are you expecting people for the N/A? Or what's the intention?

CYNTHIA POWELL: Yeah. I think that would be appropriate to use N/A, yeah. I think

I'd mentioned and we know that there are disorders that may be considered that are not enzyme related. But where it's available, I think there might be a parentheses there; I'm not sure. But "where available."

MEI BAKER: I was wondering if the purpose to -- you find a gene, you want the function marker. Can you use the other term? I don't know how it really works because in my mind I think about the SCID. I think about the FMA. If you're trying to make a nominator to define the marker -- but I think you're right. If it's not an enzyme deficiency, maybe you can just put an N/A.

CYNTHIA POWELL: Okay. Thank you.

Shawn McCandless.

SHAWN McCANDLESS: Shawn McCandless, Committee Member.

Yeah, actually my question is similar to Mei's. And that is, how would you see like CMV being listed as a proposed condition, where congenital hearing loss? It seems like we're

being more specific. And I'm not sure how things like that would be listed.

CYNTHIA POWELL: I think that it would be, you know, dependent on what the condition was, whether all of the spaces could be or should be filled out. And we may need to look again at that to just make sure that it's clarified for those who are submitting.

But I think, you know, depending on the condition, one wouldn't expect all of the areas to have information available on those.

SHAWN McCANDLESS: But even the type of disorder is not really very clear. Again, SCID or hearing loss or congenital cyanotic heart diseasehow would those be classified? And does it matter? I mean, is it going to impact anything about the review?

CYNTHIA POWELL: Um-hm. Did you want to suggest any specific changes, Shawn?

And Carla was suggesting in the chat, instead of enzyme, maybe gene product or critical measurement, critical biomarker?

(Pause)

MEI BAKER: This is Mei again. I just want to quickly -- in my head, I thought the use of biomarker is more generic.

CYNTHIA POWELL: Um-hm. Okay.

All right. Thank you for those suggestions.

Jed Miller.

JED MILLER: This is Jed Miller, Association of Maternal and Child Health Programs.

Also there on section 1, part A, severity of disease, the new content about including U.S. distribution/prevalence among phenotypes if applicable.

I'm wondering, does that mean the distribution of phenotypes is just relative to each other? Or does that mean distribution with respect to race and ethnicity and possibly geography? Just curious if that term "distribution" has anything specifically intended for it.

CYNTHIA POWELL: My understanding was

that we were not going to ask for that specific information. But Alex may want to comment.

ALEX KEMPER: I need to find my unmute button. Yeah, they were just getting a sense of what the epidemiology is. I hadn't gotten -- I apologize, but maybe just referring to it just as the epidimiology, the condition in the United States.

CYNTHIA POWELL: Okay. And can we just go back to the slides again? I wanted to finish up some additional things that will be included that we'll be voting on.

So the next slide after this.

(Slide)

CYNTHIA POWELL: So this was the nomination form. And then to go on to the evidence-based review process updates. To develop a systematic and transparent framework for incorporating expert-derived evidence.

The ERG will expand current procedures for assessing the gray literature and incorporate standard procedures used in GRADE to collect

expert-derived evidence to supplement unpublished evidence. Once-relevant meeting abstracts or other unpublished sources have been identified in the evidence review. If information available is not sufficient to assess quality and bias risk, the ERG will request further information from the investigators and authors.

Next, the registry data and other sources of data. The EAP meeting attendees agreed that conducting new analyses on unpublished data within the timeframe allotted for review is challenging from a timeframe standpoint, but also poses issues due to the data and analysis not being peer reviewed.

So the actionable item is that registry and other unpublished sources of data will be considered and reviewed as unpublished evidence.

Next slide.

(Slide)

CYNTHIA POWELL: Current public health system impact findings regarding cost estimates are not widely generalizable to all newborn

screening programs, especially regarding resources and costs. So, the PHSI cost assessment results will report cost estimates in general terms versus point estimate ranges.

Next slide.

(Slide)

CYNTHIA POWELL: And then finally, in terms of the decision matrix, no major changes have been done in the decision matrix. But additional guidance has been drafted to help Committee Members in utilizing the decision matrix.

And this would include the purpose of the decision matrix, then going over more detailed information regarding what is meant by "net benefit" and giving descriptions for each criterion within the decision matrix that have been thought to be too limited, especially regarding some of the complex conditions that are being considered.

So that was included in the briefing book. And at other times we've seen that.

Next slide.

(Slide)

So, the summary of the immediately actionable updates to the nomination form, the evidence-based review, assessing published and unpublished evidence, the public health impact assessment regarding cost estimates, and the decision-making process regarding the decision matrix guidance.

And are there any other comments or questions from Committee Members and/or organizational representatives?

Scott Shone.

SCOTT SHONE: Hi. Scott Shone, Committee Member. Thanks, Dr. Powell.

So, I just wanted to go back to what Shawn and Mei were saying. Are we proposing a modification to what's in the briefing book, at least on the nomination form for that segment that says "gene"? It doesn't say "if applicable"; I went back and looked.

So, I guess I'm asking, do Mei and Shawn

want to propose -- and I don't know. Maybe this is not in order. So, forgive me.

(Laughter)

CYNTHIA POWELL: No, that's okay.

SCOTT SHONE: Are we proposing to actually make a change to vote on, as opposed to leaving it as is, first of all? And I guess there's a second, I will just say. I think the rest of the changes to the form do help from an N&P perspective. As a member of the N&P Workgroup, I think that what we're asking for will help the process a lot.

But I just wanted to make sure I didn't get lost in the -- I got lost in the back-and-forth on, where do we land on those two pieces, and also with Jed's question around, are we changing it to epidemiology? I mean, where are we actually looking at on that form before we move toward a vote, please?

CYNTHIA POWELL: I think it depends on what the Committee Members think. You know, if it's just two or three fairly minor revisions, we

can state what those are and then vote on, you know, the full package with those revisions. I think if it's going to need to be more major revisions, then we probably need to delay the vote and look at additional revisions of the form.

From what I'm hearing, we had one suggested change in section 2, part A, adding the word "are" to, "Has the CDC's newborn screening and molecular biology branch been contacted regarding these, and are other validation measures currently pending where available?" And then instead of asking for the "enzyme," to change that to "critical biomarker."

In terms of the epidemiology, I'm not sure if there's specific wording changes or if people need a longer time to think about that.

And Kellie Kelm has a question or a comment.

KELLIE KELM: Kellie Kelm from FDA.

I just had comments or clarifications I could provide on how to describe most cases of executive clearance or authorization, not

approval. I can just pass along those comments to you, Cindy, and the HRSA folks just to ensure that's accurate.

CYNTHIA POWELL: Okay. Okay.

I've gotten a bunch of messages from Mia. So, I think it may help if Mia unmutes and gives us some guidance whether we should delay the vote awaiting some of these changes that we could then send out to the Committee Members, or if we should go ahead and vote with the revisions.

MIA MORRISON: Thanks, Dr. Powell.

From what I'm hearing based on Committee Member feedback right now, it sounds like these are relatively minor revisions that we could summarize today on the webinar. And if Committee Members feel comfortable, we can vote to adopt or not adopt these changes today.

If, Dr. Powell, you feel comfortable moving in that direction, I'd be happy to report the proposed modifications. And after the webinar next week, they can send out the modified nomination form.

So, I'd defer to you, but I believe based on the discussion today, we can still vote on this nomination form.

CYNTHIA POWELL: Okay. If it's okay with HRSA, it's okay with me. So, we will go ahead.

Is there a motion to either approve or disapprove the updates to the nomination form, the methods for reviewing published and unpublished evidence, reporting cost estimates, and decision matrix guidance? And Alex said there's a clarification on the cost description that we need to fit in, which is minor. Okay.

So, we'll have input from Alex and Kellie Kelm, and anyone else. So, is there a motion to go ahead with approving these with the recommended minor revisions?

MOTION TO REVISE/APPROVE UPDATED NOMINATION FORM

KYLE BROTHERS: This is Kyle Brothers, Committee Member.

I move to vote, including those minor revisions, to approve.

CYNTHIA POWELL: Is there a second?

JEFF BROSCO: This is Jeff Brosco, Committee Member.

I second.

CYNTHIA POWELL: Thank you.

Does any Committee Member have a conflict of interest regarding this vote and the need to recuse themselves?

(No audible response)

CYNTHIA POWELL: Are there any abstensions?

(No audible response)

CYNTHIA POWELL: Okay. So Committee Members, I will read your name. And if you are voting to approve the updates, please state "Approve." If you object, please say "Oppose."

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Approve.

CYNTHIA POWELL: Jeff Brosco.

JEFF BROSCO: Approve.

CYNTHIA POWELL: Kyle Brothers.

KYLE BROTHERS: Approve.

CYNTHIA POWELL: Carla Cuthbert.

CARLA CUTHBERT: Approve.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Approve.

CYNTHIA POWELL: Kellie Kelm.

KELLIE KELM: Approve.

CYNTHIA POWELL: Shawn McCandless.

SHAWN McCANDLESS: Approve.

CYNTHIA POWELL: Kamila Mistry.

KAMILA MISTRY: Approve.

CYNTHIA POWELL: Melissa Parisi.

MELISSA PARISI: Approve.

CYNTHIA POWELL: Cynthia Powell. I approve.

Annamarie Saarinen.

ANNAMARIE SAARINEN: Approve.

CYNTHIA POWELL: Scott Shone.

SCOTT SHONE: Approve.

CYNTHIA POWELL: Joan Scott.

MICHAEL WARREN: This is Michael Warren, back on for HRSA. Approve.

CYNTHIA POWELL: Oh, okay. Thank you. All right. So the Committee has voted to approve

the immediately actionable updates to the nomination, evidence-based review, and decision-making process with the minor modifications included.

Members of the public, changes to the nomination form will not go into effect until January 2022. The DFO will post the updated nomination form to the ACHDNC website within the next few weeks. Also, in early 2022, a series of consumer-friendly educational materials on Committee processes, including an FAQ on the nomination process, will be made available on the Committee's website.

If you have any questions about the updated nomination form or condition, nomination process, please contact me or Mia Morrison, the Designated Federal Official for the ACHDNC, at achdnc@hrsa.gov.

So I appreciate all of the input from Committee Members and the organizational representatives on these changes. And we'll next go on to the final thing before we break. Oh, and

I'm going to provide a feedback on next steps at the February 2022 Advisory Committee meeting.

RECAP OF KEY ISSUES IDENTIFIED FOR FUTURE CONSIDERATION

CYNTHIA POWELL: As I mentioned earlier, we will continue to consider recommendations that were generated through this process that require additional discussion, research, or policy change. In the folowing slides, I'll provide a brief recap of those recommendations.

Next slide.

(Slide)

CYNTHIA POWELL: So we wanted to establish a plan to conduct regular review of conditions on the RUSP. Decisions are needed to define this process, including the frequency of review, how many to review in a year, how often to review different conditions that are already on the RUSP.

What's the process for prioritizing review of those RUSP conditions? Should there be a nominating process, or how would they be selected? What would be other considerations and

criteria for reviewing those conditions? And then what are the goals and outcomes of doing this?

Next slide.

(Slide)

CYNTHIA POWELL: In terms of assessing long-term follow-up of newborn screening, what's the impact of newborn screening? What are the treatment and clinical outcomes, both short- and longer-term? What are the costs of the implementation and treatment?

What's the impact on the health care system and providers? And also, consideration of equity and access long-term for those infants identified with conditions?

Next slide.

(Slide)

CYNTHIA POWELL: Establishing a priority list of research and development issues, which will be ongoing, while revisiting the decision matrix, specifically regarding the B-ratings where there is a moderate certainty of evidence. And it was felt that further discussion is needed to

develop guidance regarding B-ratings.

There has been a lot of interest in discussion about determining values, values of stakeholders and others, and including this in the decision-making process. Certainly the limitations by the nine-month review make this extremely challenging, but something that we want to continue to consider.

What are the preferences for newborn screening, especially among patients, families, and the public? And then how to capture values and preferences regarding attitudes, and what are critical outcomes of these measures?

Next slide.

CYNTHIA POWELL: And that's it.

So more to come regarding those issues. And at this point we're going to break. Please note the schedule change once again. The Committee will break from 12:15 to 1:00 p.m. Eastern time. And when we return, we'll begin at 1:00 p.m. with public comments.

Thank you all. See you soon.

BREAK

CYNTHIA POWELL: Welcome back, everyone. I think we can get started with our afternoon session. It's still morning for some of you, I know.

Mia, are we ready to go ahead? Has everybody been able to rejoin?

MIA MORRISON: Yes. I would say we can go ahead.

CYNTHIA POWELL: Okay. I need to take the roll call again. So we'll start with Committee Members from the Agency for Health Care Research and Quality.

Kamila Mistry.

(No audible response)

CYNTHIA POWELL: Mei Baker.

MEI BAKER: Here.

CYNTHIA POWELL: Jeff Brosco.

(No audible response)

CYNTHIA POWELL: I think he may be a little late in coming back.

Kyle Brothers.

KYLE BROTHERS: Here.

CYNTHIA POWELL: Jane DeLuca.

JANE DELUCA: Here.

CYNTHIA POWELL: From the CDC, Carla Cuthbert.

CARLA CUTHBERT: I'm here.

CYNTHIA POWELL: From the FDA, Kellie Kelm.

KELLIE KELM: Here.

CYNTHIA POWELL: From HRSA, do we have --

JOAN SCOTT: Joan Scott. I'm here.

CYNTHIA POWELL: Joan, okay. Thank you, Joan.

(Laughter)

CYNTHIA POWELL: Shawn McCandless.

SHAWN McCANDLESS: Here.

CYNTHIA POWELL: From NIH, Melissa Parisi.

MELISSA PARISI: Here.

CYNTHIA POWELL: I'm here.

Annamarie Saarinen.

ANNAMARIE SAARINEN: Here.

CYNTHIA POWELL: And Scott Shone.

SCOTT SHONE: Here.

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

ROBERT OSTRANDER: I'm here.

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

DEBRA FREEDENBERG: Here.

CYNTHIA POWELL: From the American College of Clinical Genetics and Genomics, Max Muenke.

(No audible response)

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

(No audible response)

CYNTHIA POWELL: From the Association of Maternal and Child Health Programs, Jed Miller.

JED MILLER: Here.

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

SUSAN TANKSLEY: I'm here.

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

(No audible response)

CYNTHIA POWELL: Unfortunately, I think he's sick. So, we hope you feel better soon, Chris.

From the Association of Women's Health, Obstetric, and Neonatal Nurses, Shakira Henderson.

(No audible response)

MIA MORRISON: I'll see if Dr. Henderson is here.

CYNTHIA POWELL: Okay. Thanks, Mia.

From the Child Neurology Society, Margie Ream.

MARGIE REAM: I'm here.

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

JACOB HOGUE: Here.

CYNTHIA POWELL: From Genetic Alliance, Natasha Bonhomme.

NATASHA BONHOMME: Here.

CYNTHIA POWELL: From the March of Dimes,

Siobhan Dolan.

SIOBHAN DOLAN: Here.

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

CATE WALSH VOCKLEY: I'm here.

CYNTHIA POWELL: From the Society of Inherited Metabolic Disorders, Georgianne Arnold.

GEORGIANNA ARNOLD: Here.

CYNTHIA POWELL: Okay. Thank you.

PUBLIC COMMENTS

CYNTHIA POWELL: All right. Next we're going to have our public comment period. We received three requests by individuals to provide oral public comment to the Committee today. Committee Members received a written copy of their testimony prior to the meeting. The order that will go in is with Jhanjhi Hu, Niki Armstrong, and Dylan Simon.

JHANJHI HU: Thank you, Dr. Powell. Is it time for me to speak in here?

CYNTHIA POWELL: Yes. Yes. Thank you.

JHANJHI HU: Okay. Thank you.

Thank you for the opportunity to comment. Hello, everyone. My name is Mike Hu, cofounder of Project Guardian, a nonprofit organization dedicated to push newborn screening forward.

I'm a father of three boys. My two elder sons were diagnosed with MPS II in 2011. Over the past decade, my younger son has shown better outcomes due to his presymptomatic diagnosis and treatment, which has inspired my passion for newborn screening.

I have to apologize. I'm at the Childrens Hospital with him today for his trial treatments. So bear with me when there are background noises for announcement and what-not.

I submitted a written comment, but I'm going to digress a little bit today. In response, I want to just comment on the MPS II evidence that we have seen earlier and just some of the questions, as a parent from the advocacy perspective.

The first one is for Dr. Shone's comment on the paucity of data showing presymptomatic

treatment benefits. And I want to say that this is at the heart of all of the challenges in terms of coming up with nomination packages. This is probably the most challenging one, which is to demonstrate the presymptomatic treatment benefit.

And that is for a variety of reasons, but it's basically a chicken-and-egg conumdrum. Without really implementing screening population-wide, we cannot identify these cases and we have to rely on sibling studies, case reports to show some of the benefits. So for the quantitative evidence that we're seeking, it is not going to come.

And even though we have screening programs in Illinois -- and serious kudos to everyone who is involved in enabling that -- the slow progressive nature of the disease means it's going to take quite a few years before we can see anything quantitative. And so, you know, we're still early on in the screening process, and that's why there's a lack of evidence, if you will.

I do want to mention that in this regard, I hope -- and this is not just for MPS II, but for other diseases as well -- that when we consider the evidence, we will put the scientific rationale behind it, as well.

For something like MPS II, whereby the scientific background of how the disease progresses and how the accumulation of gas causes progressive damage in all of the organs, I think it's hard to argue that earlier start of treatment is going to be beneficial to control the GAG damage. We don't have the quantitative data to show for that. But the scientific rationale is there.

The other one is for the six-minute walk test, what the 33 meters really mean in terms of the gain. I think Dr. Freedenberg has provided some background on that.

I want to comment. As a family, when we joined the Haas study 10 years ago, this was immediately a problem to us because six minutes is just not meaningful for these boys. You can see

the clear difference between mobility on my older son and my younger son. But both of them can hike, you know, at least four miles at a time. So a six-minute walk test is just nowhere near the limit.

And even today, 10 years later, my older son can still walk about a mile. But if you see the boy himself, you will be immediately able to tell that he is severely affected. I think in this case, it's probably an inappropriate choice of metric to measure. In that regard, I think the potty train is a much better measure for future study purposes.

And the final one that I want to comment on is for Dr. Baker and Dr. McCandless mentioning the variance of unknown significance in the pilot screening programs. I think these cases are slightly different from the typical view as we hear about, because they have some priors, not entirely from healthy background. They did screen positives. So the interpretation of that is a little bit different.

And we've also heard, from Dr. Kemper's presentation, that private notations, at least in the case of MPS II, are frequently seen and hard to interpret. Right? So I think the solution to that, at least to some extent, is once we have screening, the accumulation of data will push us to better and better interpretations for future cases.

I had my comments focused on test performances for screening in terms of false positives and false negatives. While I'm running out of time, I just want to make a quick comment.

False positives, as we know, there are real reasons why we ask for high specificity. And as a previous molecular diagnostic test developer, I know exactly why we ask for that.

But at the same time, as a patient family, I think we should consider not just the ethical and social impact for false positive screenings, but also the ethics and inequitable consequences of not screening to the affected babies and families which, in most cases those are

devastating consequences.

And so the question to pose to everyone for consideration is, Can our society as a whole shoulder more such burdens, undesirable as they may be, so that the horrible impacts to the affected families and babies can be alleviated?

And last, I want to leave you with a quote from Mr. Winston Churchill. "Perfection is the enemy of progress." We know that no screening tests are perfect. Let's keep that on our minds as we pursue progresses in newborn screening for our future generations.

Thank you for your attention.

CYNTHIA POWELL: Thank you for your comments.

Next we'll hear from Niki Armstrong.

NICKY ARMSTRONG: Thank you. Can you hear me okay?

CYNTHIA POWELL: Yes.

NICKY ARMSTRONG: On behalf of Parent Project Muscular Dystrophy and the Duchenne patient community, thank you for the opportunity

to speak today. My name is Niki Armstrong, and I serve as the Newborn Screening Program Manager for PPMD.

I am pleased to provide an update about our Duchenne newborn screening pilot in New York City today. We are so excited to share that we completed recruitment on our Duchenne newborn screening pilot. Over the two-year pilot, conducted at the epicenter of a pandemic in New York City, we were able to screen more than 36,000 babies for Duchenne.

Of those newborns, 42 babies have been referred to genetic testing because the initial screen indicated increased risk. While some follow-up testing is still ongoing, after this week we have identified four boys with Duchenne or Becker, and one carrier female.

The incidence of four boys out of about 18,000 male births is consistent with past research showing an incidence of about 1 in 5,000 males.

Our pilot was conducted through a unique

model that utilized tools, resources, and expertise at PPMD, the Newborn Screening Translational Research Network, and the New York State Department of Health.

There was funding support from PPMD, and an innovative precompetitive funding consortium that comprised biopharmaceutical industry partners who all had the commitment to early diagnosis and intervention in Duchenne.

The pilot is guided by an amazing steering committee comprising representatives from federal agencies, provider groups, and from key Duchenne stakeholder communities. The pilot itself utilized the FDA-approved CK-MM assay.

Our Duchenne effort has convened experts and established the partnerships required to implement nationwide newborn screening for Duchenne. PPMD and Duchenne newborn screening program incorporates expertise from leaders within NIH, HRSA, FDA, CDC, AAP, the ACMGACHDNC, past Duchenne pilots, the boarder newborn screening community, the industry partners, and the Duchenne

community.

As you all know, a pilot is just one of the first steps in the journey to building a nationwide newborn screening system. We are deep in the trenches of the next step -- compiling the rough nomination package for future consideration by this Committee. We are reviewing the evidence from our community of spectative work in newborn screening and infrastructure development, reviewing the New York State pilot, other newborn screening pilots for Duchenne that are ongoing.

And we look forward to engaging with you throughout this over the next coming months.

While data collection, analysis, and publication of the data from the pilot are ongoing, really this effort is about changing the journey for the babies and families who are served through our newborn screening system. The families who have been identified with a child with Duchenne or Becker are now being supported by their primary providers with materials that were specifically created to help those providers care

for newborns with Duchenne.

The families were referred to expert follow-up care in the health systems associated with muti-disciplinary neuromuscular clinics. Families are being offered the option of participating in clinical trials when relevant, as well as connection and support from early intervention referral services, and advocates to organizations and families and our community.

And of course, we are going to track the outcomes of these babies and families to see how they differ from those whose diagnoses occur as a result of the typical and expensive odysseys later in childhood.

We are incredibly grateful for all of our partners, and especially the leadership within New York State. Within the state laboratories, the birthing centers, the specialty clinics, and primary provider specs, we are grateful to all of those working with us to ensure that these babies identified through this program are receiving the most immediately, expert, and comprehensive

follow-up care possible.

So today we would like to extend our gratitude to the families, experts, and partners who have helped us get this far. With now five approved therapies and a research pipeline filled with potential therapeutic interventions, newborn screening will provide optimal opportunities for care and treatment in Duchenne. Thank you.

CYNTHIA POWELL: Thank you.

And finally, we'll hear from Dylan Simon.

DYLAN SIMON: Thanks first, Dr. Powell. On behalf of Everlife Foundation and the rare disease community, I'd like to thank the Committee for providing me the opportunity to offer comments here today. My name is Dylan Simon, and I serve as the Newborn Screening and Diagnostic Policy Manager for the EveryLife Foundation for Rare Diseases.

The foundation's newborn screening initaitive is focused on ensuring that babies receive lifesaving treatment opportunities through early diagnosis by newborn screening.

One of the ways in which we work to achieve our mission is through empowering rare disease advocates to successfully navigate the newborn screening ecosystem through the facilitation of our annual Newborn Screening Boot Camp program.

The boot camp can be in partnership with Expecting Health, which has been a great partner for all of the three years we've run this boot camp. And this year it was a three-week event designed to educate and engage newborn screening stakeholders. We were delighted with the success of our virtual event with more than 230 individuals attending at least one week at boot camp.

And I would like to thank the multiple members of the Advisory Committee and MTP working group who participated in this year's event. We would especially like to recognize the members of the HRSA team and Dr. Cynthia Powell for preparing and delivering a thorough review of the upcoming changes to the rationalization and evidence-review

process.

Other topics covered in boot camp include overviews of the overall newborn screening system, opportunities for adjusting racial inequities within newborn screening, and the process of adding conditions to the Recommended Uniform Screening Panel. This was a rare one-off opportunity for many in our community to actively engage with newborn screening symptoms to bring more insight with the impending updates. Thank you for the time you took to engage with us.

In closing, over the past year I and other representatives of the EveryLife Foundation have shared their perspective of our community encounters and working group partners on such topics and creating essential databases for longitudinal studies, challenges in conducting pilot studies, not sacrificing the patient review when it comes to updating pacer, you, or updates to the evidence review and nomination process.

Today our minds will focus on the areas of education and opportunities for a continued

community engagement. As you know, revisions to the interview process will impact stakeholders across the newborn screening system, changes to the data requirements will impact the design of studies conducted for a RUSP nomination package.

Any review of the current RUSP conditions will require additional oversight and data reporting for state and western programs. For these reasons, we suggest the Advisory Committee prepares a suite of educational materials for newborn screening stakeholders, identify changes that have to be processed and how those changes impact specific components of the newborn screening system.

It was great to hear earlier Dr. Powell talk about these materials already in development, and we look forward to that.

To accomplish these goals, we do encourage the establishment of a Multi-Stakeholder Working Group including our -- patient community to inform the development and implementation of these materials. We were happy to provide

resources for the development of an FAQ document for nominators, and we look forward to supporting the creation of additional materials.

We are grateful for the opportunity as a community to continue to provide input, and encourage those community teams to solicit input from multiple stakeholders by having proposed updates that will impact the various stakeholders' needs.

Thank you again to the Advisory Committee for your tireless efforts on behalf of our nation's newborns. We are encouraged by all the great work that is occurring in the newborn screening space and look forward to continuing to help advocate and effectively navigate engagement with the Committee. I thank you so much.

CYNTHIA POWELL: Thank you.

Thank you to all of you for your written and oral comments.

We're now going to go on to our last presentation of the day. This will be from Dr. Melissa Raspa, who is a senior scientist and

Director of Genomics, Ethics, and Translational Research Program at RTI International.

She will discuss the HRSA newborn screening portfolio evaluation, exploring current and future needs of the newborn screening system, in part through conversations with state newborn screening programs.

Much of Dr. Raspa's career has focused on understanding the needs of individuals with intellectual disability and their families, especially those with fragile X syndrome, and more recently Rett syndrome.

She serves as a co-investigator on Early Check and leads the RTI team on a new award from the Eunice Kennedy Shriver National Institute for Child Health and Human Development to conduct a pilot study on mucopolysaccharidosis type II.

She is the project director for a study funded by the Centers for Disease Control and Prevention which provides support to the North Carolina Newborn Screening Program and follow-up team to expand the state's screening to include

SMA, X-linked adrenoleukodystrophy, mucopolysaccharidosis type I, and pompe disease.

Dr. Raspa.

HRSA NEWBORN SCREENING PORTFOLIO EVALUATION: CURRENT AND FUTURE NEEDS OF THE NEWBORN SCREENING SYSTEM

MELISSA RASPA: Thanks, Dr. Powell. I'm hoping my slides are going to come up here in a minute. Let's wait for those.

And while we're waiting, just a special thanks to HRSA for the invitation to present today to the Committee about some of our findings from the newborn screening portfolio evaluation. So there's lots to present today, and I'm hoping to hit some of the highlights over the next 25 minutes or so, and then leave some time for questions.

(Pause)

MELISSA RASPA: I'm not seeing the slides. I don't know if you all are.

MIA MORRISON: No, I'm not seeing them either, Dr. Raspa. Are you able to locate those slides?

MELISSA RASPA: Yeah. It says it's sharing from the screen, but I'm not seeing it being shared. So I'm going to try resharing a couple of times.

MIA MORRISON: Okay. Thank you.

(Pause)

MIA MORRISON: I still don't see them.

MELISSA RASPA: So I tried sharing my screen.

(Pause)

MIA MORRISON: Yeah, we still can't -- oh, they're on. They're on.

MELISSA RASPA: Okay.

(Laughter)

MELISSA RASPA: There we go. The slides show perfectly. Okay, great. Well, you can click to the next slide.

(Slide)

MELISSA RASPA: Okay. So just to get us started, last September HRSA ordered RTI a contract to evaluate, among other things, their newborn screening portfolio of programs.

Here we see the purpose of the evaluation, which was to understand the needs of the newborn screening system and its stakeholders; the unique role that HRSA programs play in addressing those needs; and also the unmet needs of the newborn screening to help inform future programs.

You can click to the next slide.

(Slide)

MELISSA RASPA: There's a lot, and I'll walk you through it. So we shift the evaluation around the goals of a newborn screening system, as was specifically described in the Newborn Screening Saves Lives Reauthorization Act of 2014.

So there are six goals in all stated in the federal legislation. So that first goal, goal one, is kind of our broad, overarching goal, whose aim is to enhance, improve, or expand the ability of states to provide screening and counseling. Goal 2 next focuses on the provision of education and training and technical assistance to both lab personnel and other health care professionals.

Goal 3 really centers on follow-up and treatment by seeking to establish, maintain, and operate a system that aims to assess and coordinate services. Goal 4 is the timeliness goal of newborn screening, including starting with specimen collection all the way through diagnosis.

Goal 5 is specific to families and other consumers, and seeks to develop and provide education to these stakeholders. And then that bottom goal, Goal 6, is where the ultimate goal of newborn screening is and aims to improve health equity and health outcomes, reduce morbidity and mortality for all individuals and families through the provision and improvement to the quality of services.

So we'll use these six goals throughout the presentation to kind of really explain the project and the results.

Next slide.

(Slide)

MELISSA RASPA: So the evaluation focused on just six of HRSA's current or former newborn

screening programs. And the six programs are listed here.

So the first one is Newborn Screening Data Repository and Technical Assistance Program, also known as NewSTEPs; the Quality Improvement in Newborn Screening Program, also referred to as NewSTEPs QI; Newborn Screening Family Education Program; the Newborn Screening State Evaluation Program, which was money directly provided to states; The Newborn Screening Implementation Program Regarding Conditions Added to the RUSP; and then finally, the Improving Timeliness of Newborn Screening Diagnosis, which is known as NewSTEPs 360.

Next slide.

(Slide)

MELISSA RASPA: Okay. I'm going to walk you through our evaluation methods, and on the next slide you'll see also our evaluation questions.

(Slide)

MELISSA RASPA: So these are four

evaluation questions that I'm really going to focus on today. We had others, but these are the most appropriate to focus on for the Committee.

The first question there you can see is, To what extent has the portfolio of programs as a whole contributed to achieving HRSA's overall newborn screening program goals?

The second is, What are the current needs of the newborn screening system?

The third, What are the unmet needs or gaps that currently exist in HRSA's portfolio?

And finally, What are the expected needs of the newborn screening system in the future?

Next slide.

(Slide)

MELISSA RASPA: Okay. So we use both primary and secondary data as part of the evaluation.

So for the primary data collection, we engage with 52 stakeholders from a variety of different groups including program grantees, newborn screening program staff, both lab and

follow-up folks, parents, representatives from patient advocacy groups, clinicians and subject-matter experts.

So for 32 of these stakeholders, we conducted indvidual interviews that lasted about an hour each. And then the remaining stakeholders participated in one of six different focus groups. Those are a little longer, about 90 minutes each.

For the secondary data, we reviewed grantee-reported materials and obtained some data from outside sources, including timeliness data from NewSTEPs.

We also conducted a scoping review of the newborn screening literature based on literature that was published in the last 10 years. Over 700 articles were found and assessed to determine whether or not to include. In the end we included just over 100 full-text articles in our review.

We also did an environmental scan of newborn screening websites and different partner organizations such as Baby's First Test and even information that was posted on the Committee's

website.

Next slide.

(Slide)

MELISSA RASPA: Not surprisingly, we had a wealth of information. These two pieces are these two sources of data. So I'll just walk you through our analysis approach.

So first, the interviews and focus groups were recorded and then later transcribed for analysis. Given the quick turnaround that we had and timelines on the project we really wanted to use what's called a "rapid turnaround analysis technique" to help really distill that information.

So we created an Excel template that helped to organize all of the information from the interviews and the focus groups.

We then took the notes and the transcribed transcripts and used what is called a tagging procedure. And it's similar to what you were doing in vivo to code the data. We looked for overall themes, but then aligned it with the

newborn screening goals that I mentioned, the six goals, and then the evaluation questions.

Next the team summarized the findings both within the stakeholder groups and then across the stakeholder groups. And finally what we did was kind of merge the information from the primary data collection with the secondary data collection. And we had similar templates and forms that we used to kind of extract data from the review and the environmental scan.

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(Slide)

MELISSA RASPA: As I mentioned, and I'll walk you through, there's a lot of the evaluation findings. Like I said, it's organized by the six goals of the newborn screening system.

So for each we're going to start with kind of this overarching slide that provides like a high-level summary. And I've also included a quote from one of the stakeholders to really describe how well the program, again, the newborn screening portfolio, is achieving its goals.

And then on subsequent slides, I'll talk about the kind of future needs that we're waiting to provide to the stakeholders, as well as some potential solutions to address those gaps.

(Slide)

MELISSA RASPA: Here you see Goal 1. Again, this is that overarching goal to enhance, improve, or expand the ability of states to provide screening, counseling, and health care services to newborns and children. And overall, HRSA's programs have really made tremendous progress in creating a more efficient and proficient newborn screening system over the years.

In particular, HRSA's funding has helped to really support states to expand their newborn screening panels. They include conditions that have been recently added to the RUSP.

You can see there on the right-hand side is a quote from one of the stakeholders: "I don't think we could do what we do [without HRSA programs]. They're the ones that help us move it

forward. They connect us with other states. They provide us with screening algorithms . . . I would say these programs are our go-to on screening."

Next slide.

(Slide)

MELISSA RASPA: Despite this, there are still some current and future needs that were raised during those discussions with our various stakeholders. I listed several here. So first, the first theme here is that really there's a need for additional federal guidance to help improve what one stakeholder called a "patchwork" system on newborn screening.

In particular, stakeholders mentioned discrepancies across states, as well as duplication across states that would really need some additional federal guidance to help better understand and connect to the system as a whole.

The second needs was the ability of state programs and the newborn screening system as a whole to really keep pace with new treatments and screening technologies.

In particular, stakeholders were really concerned about the feasibility and readiness of states to implement these conditions, especially things like sequencing techniques and states, as they become more readily available. And subsequently, also access to new treatments and therapeutics by identified babies and their families.

Finally, stakeholders highlighted the need for enhanced data interoperability. Many stakeholders really spoke to the need for a better public health informatics infrastructure in order to increase efficacy and testing accuracy and really improve outcomes all throughout the newborn screening system.

Next slide.

(Slide)

MELISSA RASPA: So some potential solutions that were mentioned by stakeholders to address these gaps and needs included better collaboration among all federal agencies and different funded programs that have a stake or

focus on newborn screening. So not just HRSA, but all programs and all federal agencies.

A second potential solution was an increase, as I said, in federal guidance to really help reduce state-to-state variability, including -- specifically mentioned was guidance on how quickly states should begin screening for new conditions once they're added to the RUSP.

A lot of the state-to-state variability was around how quickly conditions get added to the RUSP across different states.

Another potential solution focuses on investments in expanding the newborn screening workforce. Not a surprise to a lot of people on this call, lots of different options, both direct support to states, training programs for students, certification programs for providers, and also possibly incentives for staff who are currently working in newborn screening.

For example, someone mentioned something similar to the NIH loan repayment program for folks.

Another possible solution that would really kind of complement this evaluation that we did at the federal level was to really focus on state-level evaluations of individual programs, newborn screening programs at the state level. That could include conducting an evaluation or a needs assessment in order to really assess effectiveness, define needs, and determine improvement plans.

If I didn't mention that in today's call already, there's some talk and discussion around reviewing possibly revising the RUSP review process.

And then finally, the final solution was related to Goal 1, was to provide direct support to states to really help with some of these differences across states. And it would really help to limit fee increases, buying new equipment, and in general support staff.

All right. Next slide, to Goal 2.

(Slide)

MELISSA RASPA: Okay. So this one again

is to remind you of the provision that education, training, and TA to lab personnel and other genetics and health care professionals. So overall, HRSA programs have provided strong support on training and TA for lab and follow-up staff. Again, especially related to timeliness, adding new conditions to state panels, and the NewSTEPs data repository.

However, one area that has had a little less focus is education of health care providers. You can see the quote there on the right: "HRSA's newborn screening programs are making huge efforts to provide education and training and TA; it's continuous and every month. It's unprecedented the amount of time and energy spent, even during this past challenging year, to provide opportunities for people to enhance their skills and move forward with different projects, whether in the laboratory or with education and training."

Next slide.

(Slide)

MELISSA RASPA: So despite all those

successes, there were some current and future needs mentioned by stakeholders in relation to Goal 2. So these are the two big-bucket themes. Additional training and TA for state staff was mentioned, both lab and follow-up.

And some particular topics that were mentioned by stakeholders included data anlytics, guidance on how to add new conditions to the state panel, long-term follow-up, and data collection methods, among others.

In particular, several stakeholders mentioned that there are some smaller or maybe under-resourced states that may need more TA than the other states who are larger or more well-equipped.

A second training and TA need was again targeted specifically around health care providers. Some more information is needed to help educate providers around newborn screening, how to communicate with families after a positive screening. Providers also need education and training about new RUSP conditions, including what

resources are available and what steps the family should take next.

Several folks mentioned we need a possible way to address some of these needs. This is maybe through an increased awareness of currently available resources, including the Communication Guide that's on the ACHD website, and sheets are provided.

Next slide.

(Slide)

MELISSA RASPA: Okay. So here are a couple of potential solutions to address the gaps and needs. First, not surprisingly, provide training and TA to a variety of stakeholders around a variety of different topics.

For example, specialists could be provided with more information about confirmatory testing and follow-up guidance. Hospital staff could receive training on how to collect dried blood spot specimens. And lab staff need continued support on new screening methods, evaluating cutoffs, and communication with follow-

up staff.

In addition, a second potential solution could be the rethinking of different models and methods for providing training and TA. For example, one suggestion that was offered was that states who receive funding as "early adopters" could serve as formal mentors to those who receive kind of the next round of funding. So they can have a train-the-trainer type approach.

Specifically targeting PCP's for the use of CME's or maintenance of certification credits was also mentioned as a potential strategy.

Next slide.

(Slide)

MELISSA RASPA: Okay. Moving on to Goal 3. Again this is really the long-term follow-up and treatment goal by focusing on establishing and maintaining and upgrading a system to assess and coordinate follow-up and treatment. So overall, HRSA's newborn screening programs have really played a key role in the success of short-term follow-up, but more work can be used around long-

term follow-up.

And you can see the quote there from one of the stakeholders that said, "Funding alone can't support the weight of Goal 3."

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(Slide)

MELISSA RASPA: So we heard a lot around this goal in our conversations with our different stakeholder groups, both current and future needs. And again, we kind of distilled them down to these two big themes. So first, there's a need for a national long-term follow-up system. However, many stakeholders whom we talked with really talked about the challenges associated with establishing such a system.

An example would be a lack of clear definition of long-term follow-up, limited guidance on who's responsible for collecting those data, how best to integrate long-term follow-up quality indicators with other metrics that are requested for the newborn screening, and many, many others.

The second area of need was really again just kind of a larger theme that we heard throughout the goals was that kind of inconsistency across states and that state variability, in this case with regard to short-term and long-term follow-up.

So as I was mentioning earlier, primary care providers often lack that knowledge about newborn screening and new conditions. And there are extensive differences both within and across states and how families are contacted and subsequently followed within newborn screening.

In particular, their access to specialists, the provision that's condition-specific information, and really helping families get connected with psychosocial supports.

Next slide.

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MELISSA RASPA: The two potential solutions that were offered up during our discussions on ways to address these gaps and needs, first stakeholders recommended the creation

of a long-term follow-up system to really help track outcomes.

It's important to mention that this could be done in collaboration with other federal agencies, or even patient advocacy groups who have similar efforts underway, including condition-specific registries that we heard a little bit about this morning with MPS II.

A Center of Excellence could be created to help support this long-term follow-up system, and investments could be made in the collection, maintenance, and use of this system to really maximize its utility.

The second solution really focuses on coordination of treatment and support for identified infants and their families.

So examples of potential solutions here could include providing conditions-specific guidance on long-term follow-up, linking families to patient advocacy groups to meet their emotional and information support needs; and creating a clearinghouse of resources for clinicians and

families about topics such as insurance coverage and educational needs, such as early intervention.

Next slide.

(Slide)

MELISSA RASPA: Okay. Goal 4 focuses on the timeliness of newborn screening systems or newborn screening in particular. And this was really seen as a really huge success story by many stakeholders. HRSA programs were really attributed to making significant improvements in timeliness over the last several years.

And as you can see in the quote there on the right, one stakeholder said, "I believe without NewSTEPs360, I don't think we would be where we are now."

Next slide.

(Slide)

MELISSA RASPA: So again, despite these successes, there were still some gaps. So current and future needs around timeliness included first kind of the need to continue to focus on timeliness and not give it up, even though some of

these achievements have been made, including a focus on quality improvement.

So even though states, as I said, are meeting these quality indicators, many states are, there's a need to maintain timeliness standards through ongoing education, quality improvement, and really funding.

Next, if data are needed beyond just the confirmatory diagnosis, to know how quickly babies are getting into treatment and whether or not that's happening on a timely manner.

However, many stakeholders mentioned that a lot of these things are dependent on the conditions. And one nuanced look at timeliness goals by their specific conditions, especially those that are more time-sensitive, like SMA, might be needed.

And then finally, as has been echoed elsewhere in the top providers often lack that education around timeliness. And some states really need additional support.

Next slide.

(Slide)

MELISSA RASPA: Okay. So possible solutions to address the ongoing needs related to timeliness include additional support to improve the timeliness of diagnosis and treatment, but providing specific metrics for different conditions.

Providing funding, training, and TA on data entry and for the NewSTEPs data repository in order to reduce burden on states and minimize data entry errors. Provide training and education to help the providers on timeliness through the use of practices such as grand rounds, personal stories or other types of methods.

And then finally, continue to support the states to address those timeliness issues related to specimen collection, transportation of dried bloodspots to state screening labs, or other screening quality indicators.

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(Slide)

MELISSA RASPA: Thank you.

Okay. Moving on to Goal 5, again this is looking at education for families and other consumers. We found that both current and previously funded HRSA programs have really increased the amount and quality and availability of educational resources. And interestingly, these resources are really perceived by many to be really high-quality.

However, one of the things that we heard from stakeholders was that some materials may lack visibility or might not be getting into the hands of people at the right time.

You can see the quote there again on the right: "We probably lean on them [HRSA] for a lot of our parent education. They've been able to give us some documents we can actually put our own state logo on, so we don't have to be the subject-matter experts, which is great. The ability to use that information and provide it to families has been very helpful."

Let's go to the next slide and talk a little bit about current and future needs related

to Goal 5, again focusing on education of consumers.

Next slide.

(Slide)

MELISSA RASPA: We heard a couple of these different things here. First, additional work is needed on how best to disseminate materials, both that information is sent to families from the prenatal period all the way to postnatal.

Stakeholders also mentioned the format, tailoring, consistency of the materials. Not surprisingly, we all know many parents typically seek out information after testing positive, online, and there was really a lot of attention paid to the need to make sure that material that families are finding is of high quality and has a good consistency of cost base and are accurate.

Additionally, stakeholders mentioned that there is a need to tailor some materials to specific types of consumers and groups.

Next slide.

(Slide)

MELISSA RASPA: Okay. There are solutions that were offered up by the stakeholders around Goal 5 or really around developing materials that can target and reach diverse groups of audiences, including creating materials that are relevant, like I said, at different points in time.

A big focus was on thinking through effective dissemination strategies to really help with that increased visibility of material. Stakeholders mentioned some of these kinds of hard-to-reach stakeholder groups such as OB/GYN's, primary care providers, and other specialists who have really been historically hard to reach, but there need to be some creative strategies in order to get that information out into the most appropriate hands.

Parents and consumers are also needing more education on conditions that have been recently added to the RUSP. But partnering with different advocacy groups is a potential avenue

and should really help with that development dissemination of educational material.

Last goal, moving on. Next slide, to Goal 6.

(Slide)

MELISSA RASPA: As I said, this is kind of that ultimate goal of newborn screening, to help improve health equity and outcomes for all individuals with genetic conditions.

So, HRSA continues to make improvements in health equity and health outcomes through a variety of different avenues, in particular providing support and training and TA to different stakeholders and really educating different, diverse groups of families, especially those from medicine-underserved populations.

Next slide.

(Slide)

MELISSA RASPA: However, there is still work to be done. So a couple of the current and future needs that were mentioned by stakeholders include challenges related to the cost of and

access to care. Differences in insurance coverage for treatment of certain conditions, and equitable access to specialists were two things mentioned in particular.

Difficulties in connecting families to social support, especially those from underserved populations, also was a theme that we heard as current and future needs, as well as systematic racism and implicit bias that might be creeping into the system kind of later on for certain families.

There is also the need for additional training and support to make sure that stakeholders were getting the information that they need to really help and address those differences between states.

Next slide.

(Slide)

MELISSA RASPA: So the potential solutions that we heard from stakeholders around Goal 6 to fully address health equity and outcomes first centered on education and training. In that

first bullet, you can see specifically around implicit bias and structural racism. It would really be beneficial for a variety of different newborn screening professionals.

Several folks under bullet 2 there mentioned that the creation of a long-term follow-up system would really help to track health outcomes and really know whether or not there were any health inequities kind of further on down the line in relation to kind of error in treatment for specific groups of people.

In addition, there was a need for additional support and coordination for families in accessing genetic services in treatment, especially, like I said, there are some underserved populations. And in particular, the next-to-last bullet, for non-English-speaking families.

Then finally, as mentioned earlier, creating some quality metrics would really help to understand how newborn screening programs are being effective on down the road with long-term

follow-up and treatment to understand whether or not the health outcomes are being achieved.

Okay. I've just got a couple more slides. The next slide can advance here. I just want to share with you all.

(Slide)

MELISSA RASPA: Some really are high-level recommendations that we synthesized all of the information that was provided from these stakeholders and couched them into these kind of three broad heads of recommendations.

(Slide)

MELISSA RASPA: The first one that we see here is the policy recommendations that we had. And so first and foremost, it seems clear from all of the data and all of the information that we really need to make sure everyone's on the same page around kind of a strategic plan for newborn screening.

In particular, one that identifies specific goals and addresses the gaps and needs that were discussed today and mentioned by the

stakeholders. That plan should really be created not in a silo, but with a variety of different newborn screening experts and different federal agencies so that it's applicable across the board.

The second policy recommendation was around the state-specific evaluations. We really felt like that would be valuable information to individual states, not just kind of a broad walk across the federal programs. That some states might find it beneficial to view a needs assessment or more of a process evaulation to really identify areas for improvement and help them to think through and prioritize next steps.

Finally, one of the big themes that we heard was the variability. Despite the RUSP and the federal guidance on newborn screening, there's still just a lot of state-to-state variability and implementation of newborn screening.

And one of our policy recommendations is to help to continue to support states directly, to implement those new conditions, and provide funding through avenues such as the Title V block

grants or even planning grants to help make it like a two-stage approach for those states who aren't quite ready to implement quite yet.

Next slide.

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MELISSA RASPA: Our infrastructure recommendations were these two. So first and foremost, again kind of reflecting back on some of the findings from Goal 3 was to create a long-term follow-up registry or system in order to track outcomes.

But again, importantly, we don't want to duplicate existing efforts or front conditions specifically, but rather kind of think at a broad scale about how that should look.

Continued focus on interoperability. I mentioned that kind of early on under Goal 1. But that was definitely something that needs to be a continued need for states. It really, like I said, helps support their infrastructure, not only to develop plans, but then also implement the plans.

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MELISSA RASPA: Finally, our practice recommendations included again a big continued focus on training and TA. Timeliness again was also kind of important to states despite the successes. Things like tiered levels of support, depending on states' needs, and really helping kind of think through creative ways to provide that training and TA for states or underserved states that are kind of harder to reach.

Then finally, our final practice recommendation was really what we termed wraparound support for RUSP conditions. And that can start with adding a new condition to a state panel, but then taking it on through the newborn screening. Educating health care providers, both primary care providers and specialists, about new conditions. And then really helping to connect families to services and supports to really meet their information and emotional support needs.

With that, the last slide.

(Slide)

MELISSA RASPA: I just want to say thanks, first and foremost to HRSA for our funding. It's been a pleasure working with them over the past year on this project. I also had a great team of staff at RTI, a very large and dedicated team who went above and beyond to meet all of our timelines.

I also wanted to give a special thanks to not only the Committee Members, many of whom are our stakeholders, but then all of our stakeholders, who really were so eager to provide such rich information that really made this a great project to be working on.

So with that, I can stop and open it up to some questions.

CYNTHIA POWELL: Thanks very much, Dr. Raspa. We appreciate your summarizing this project to do portfolio evaluation.

We'll now open it up for questions. As usual, first from our Committee Members, followed by organizational representatives. Please use the

raise-hand feature and remember to unmute yourself and state your first and last names each time you ask a question or provide a comment so that we can record things properly.

First we'll go to Joan Scott.

JOAN SCOTT: Hi, everyone.

Thank you, Melissa, for that great presentation.

I just wanted to add a qualifying comment about the slide around resources and availability of Title V just to remind everyone that Title V funds are at the discussion of the states. They are done by what the state needs, and it has to support the broad maternal/child health priorities in their states.

So the amount of that funding may or may not be available for newborn screening, at any rate significantly, in any state.

CYNTHIA POWELL: Thank you.

We can go to Robert Ostrander.

ROBERT OSTRANDER: Yeah. Hi. Thanks. Robert Ostrander, organizational rep for the AAFP.

I want to talk a minute about, and give you some insight into a family physician, and probably applies to pediatricians. So those definitely want to comment differently.

What our education situation is may be informed, some approaches you might take to address the sort of gap there, which I'm very aware of. In much of what I've been doing as the organizational rep for this group -- and I also am the organizational rep for the inter-specialty collaborating committee of practitioner education and genomics in general -- is to try to break into the various educational avenues we have through the academy.

And we're competing with a lot of other things for educational opportunities. And our day-to-day members, these things they encounter relatively infrequently are often not at the top of their list for something they need CME for.

So I don't think we're going to be very effective in focusing on just, you know, CME activities that carry some CMA credits with it,

because again everybody is pushing that on our members, and they all feel a bunch of gaps.

On top of that, at least in New York and I think some other states, there's a whole slew of hours of mandatory CME we have to do all the time because the legislative response to every sort of socio-medical issue is to require mandatory education. And we have them on opioids, we have them on bloodwork passages. We have them on human trafficking, we have them on child abuse.

And so a lot of the CME hours of the sort of sit-down sort get sucked up that way.

I think it's important to understand that for most practicing family physicians, for the more unusual conditions, a lot of their education is done POC, point of care, at the time it comes up. So we need to embed this education in the places that family doctors look.

I also sit on the ACT Sheet Advisory Group, or the ACMG. And I'm a big fan of what we've done with those and what we continue to do with those, and getting people to point it to them

when they get their patient's newborn screening test's abnormal results.

Because I think it provides pretty quick, succinct information. But I don't think it pops right up when doctors go where they go. So, you know, UpToDate is a huge resource that lots and lots of primary care doctors use. If you go to the newborn screening page, you'll find the ACT sheets listed on there near the bottom. Alex Kemper wrote that article, so maybe you can move the ACT sheets closer to the top when he does his revision.

But more importantly what's going to happen is doctors are going to go on the condition-specific thing. And I don't know how we embed the sort of quick down-and-dirty approach to an abnormal screening test, where these conditions aren't on the RUSP. But that's what people need at the point of care.

If we pointed to an ACT sheet or other specific thing in the article, whether it's an UpToDate or on medscape or one of the other

services that doctors use regularly. But I think that's going to be our challenge is to figure out how to make this stuff pop up with whatever search engines the primary care doctors use when they're confronted with this.

Because I have a hard enough time convincing the academy and all of these various evidences, whether it's the journal or the meetings, to do something on genetics in general. I mean, I finally got a pharmaco-genetics one in this year. But expect to get a big piece on newborn screening in more than very infrequently, and then have people look at it, it's going to be an uphill battle.

So that's kind of my insight just for this education workgroup or whoever is going to work on this, thinks about ways to enhance primary care physician education. Thank you.

CYNTHIA POWELL: Thank you.

Melissa, did you want to comment?

MELISSA RASPA: Yeah. I agree with many of the points Dr. Ostrander made. You know,

certainly we hurt not only for families, but for providers. It's quite a challenge, right, in trying to get them to put their attention to this one thing. And certainly at that, point of care is a great strategy.

I think it's like he said, trying to figure out how to do that. That's kind of a little bit of a puzzler. You know, I always say I'm not a trained clinician; I'm a researcher. But I think about, what is the clinic going to do when they have a patient come into their practice with cancer? How do they know where to turn to for information or how to put them in touch with the specialty teams that really treat cancer?

So some of those kind of thinking along the lines of what happens normally, I don't know if that will provide any insights into newborn screening. But it certainly might be something to consider.

ROBERT OSTRANDER: That's more or less what I said. They go to UpToDate, and they, you know, plus or minus contact. They're regional

specialists. And I think both here would probably in general would maybe reach out to their neonatal specialist depending on how remote they are.

But, I mean, that's the normal workflow. And I think you need to embed your education projects into normal workflow.

CYNTHIA POWELL: Natasha Bonhomme.

NATASHA BONHOMME: Natasha Bonhomme, org rep for Genetic Alliance.

Melissa, kudos to you for doing so much in such a short amount of time, in what, a little less than a year or so? There's so much information here I feel like we probably could have spoken for a lot longer. So thank you for this. This is really helpful.

I have a couple of comments and questions. And this goes a little bit to what Bob was just saying. In the conversations you were having, talking about reaching providers and things like that, was there any indicator that the stakeholders you spoke to were particularly an issue when it comes to newborn screening or part

of that broader health care, reaching providers who have the list that Bob just said?

I just wonder if there was any distinction that came up in the conversations you were having?

MELISSA RASPA: Yeah. It's a great point, and, you know, I will couch it in we were specifically asking about newborn screening, you know, in many of our questions. With that said, stakeholders did mention, kind of asked us about genetic services more broadly at times.

We kind of pressed on that a little bit kind of in other reports, parts of the report. But I didn't really mention it much today. And like you said, there are some more issues across the newborn screening to genetic services.

NATASHA BONHOMME: Great. Thank you.

My next comment/question, we'll see how it comes out. There is discussion that you presented in terms of people saying that it would be really great and helpful for families to have this information as early as possible, you know,

really before they are even entering the newborn screening system.

And at the same time, a lot of comments and potential solutions about really relying more on patient advocacy organizations and using their networks.

So to me that sounds a little apples-and-oranges in terms of different types of parents with different experiences who are engaging in the system a bit differently. Did those differences come up in your conversation or were parents and families talked about as one big umbrella as opposed to, you know, the parents of the 3.8 million who all go through newborn screening compared to the ones who really have a newborn screening story, as we tend to think of it?

MELISSA RASPA: Yeah, yeah. Great point. I think parents, pregnant moms in particular who haven't gone through newborn screening were talked about a little less. Given that again we were kind of focusing a bit more on newborn screening in particular.

But to me, I think some of the kind of things that we talked about in the slides would apply for those moms as well. It's kind of the timing, but also in particular the carrying of the messaging. Now, how to reach them is the challenging part that I'm sure you are familiar with, we're familiar with.

So our early check work, how you get the attention of a pregnant mom to talk about newborn screening is really challenging. Whereas on the other end of the continuum, you know, a screen positive, is really I think where those patient advocacy groups and condition-specific type things came into play, connecting families with those sets of resources, helping think through what information those families need once they have either a screen positive or their child has been identified with a specific condition.

So we heard more on that end of the continuum than we did on the front end, for sure.

NATASHA BONHOMME: Okay, great. And two more points, I promise.

One is, in the different sections, for most of them you talked about funding and the theme of increasing funding or really continuing the current models, the funding states, and having that support there. But I didn't necessarily see any language around funding when it came to education.

Is that just that it didn't hit the slides? Or people didn't really talk about that in the same way?

MELISSA RASPA: That's again another good question. I'd probably have to go back and look and see. I think it's probably just the way I spoke about it. I think across the board people talked about continued support and usually in the form of funding for all of the goals.

Even like I said, the timeliness goal, people were very loud and clear. Like, "Don't forget about it. Just because we've achieved this goal doesn't mean that we should just kind of move on and not focus on timeliness anymore."

So I think it was probably just not as --

I didn't highlight it probably as much in the slides.

NATASHA BONHOMME: That's okay. You had a lot to go through. I was just wondering on that interesting -- especially since a lot of the education components weren't about content creation, but dissemination and really getting out there. And we know how that can really be tied to finances and resources.

And then my one last point, and I really appreciate the fact that there's a whole section around health equity and all those really great suggestions of what can happen. I think that's critical, and there were some really good suggestions.

And just one piece too, I think a lot of times -- and this isn't just a newborn screening thing, but I think sometimes we think of implicit bias and things like that creeping in.

And I just kind of call to this group to think about it's not only something that's creeping in, but that really has been baked into

our health care system, especially for those who tend to be excluded from a lot of services, and just the importance of thinking about that and that frame of reference.

But thank you so much for a really great persentation.

MELISSA RASPA: Thank you.

CYNTHIA POWELL: Thanks.

We'll take Susan and then Debra next. And then I think we'll need to cut off our discussion for today.

Susan Tanksley.

SUSAN TANKSLEY: Hello. Susan Tanksley, organizational representative with the Association of Public Health Laboratories.

I just wanted to key in on a few things, and I'll try to be brief.

In regard to timeliness, I really appreciate the mention of looking at post-analytic measures. When we had the Timeliness Workgroup years ago and we came up with the pre-analytical and the analytical metrics, we mentioend at that

time that we really did need to focus on time to treatment, time to intervention, you know, what happens after the results are given to a health care provider.

And I think that that's still critical and that's really where we can make improvements still in the system.

In addition to that, it's already been mentioned a little, but education earlier to families. That's really been something that we've talked about for years and years, the need to get information to parents in the prenatal period, make sure they understand newborn screening and are able to understand what it is and what it's not so they can make better choices versus learning about it or not even learning about it when their baby's actually screened.

And I think that that continues to be really important and would be helpful to the entire newborn screening system.

And then, I appreciate the continued emphasis on training and technical assistance

throughout the system as well. In newborn training programs, it's wonderful to have the funding that focuses on those things, because there's often not that opportunity within our programs. So when there's grant funding or other programs through CDC or APHL that come down, it really is helpful for our programs.

Thank you.

MELISSA RASPA: Yeah, and I will just note that after we broke the report, we hosted some stakeholder engagement sessions last summer. I didn't really mention those, but it was really to share some of this information and kind of probe on a couple of other constructs with state newborn screening staff, again with Lab and Follow-Up.

And funding the states was one of the things that was really mentioned and some of the pros and cons, right, of doing that. But certainly there was no lack of need for or mention of, let's continue training and TA. So, how to do it I think is the quesiton.

CYNTHIA POWELL: Debra Freedenberg.

DEBRA FREEDENBERG: Thanks.

I'm going to take this from two perspectives. One is representing the American Academy of Pediatrics, and the second part of this is also on the ground at the state level. And Bob is right; most physicians will do points of care when they need the information. These are rare conditions. They are not something that a lot of pediatricians and primary care providers run into day after day.

That being said, the American Academy of Pediatrics does support newborn screening, although of course we have to kind of jockey for position for education or for national education, have the genetics and newborn screening part of that. But it is very supportive of newborn screening and is constantly published in newborn screening articles and journals. And they have a very strong support system for that.

The second part of this I'm going to take from the state level. And our state has invested

tremendous amounts of energy in education. We've tried the prenatal route and haven't had much success with that. We as a state, our follow-up is internal to us. So for every out-of-frame screening, that goes out. They get a call or a fax. They get the ACT sheets, and we have some Texas-specific ACT sheets as well.

So we have a touchpoint with every screen going out with the provider, in addition to providing them with regional resources for the specialists there as well.

And we see a great diversity of responses. As you can imagine, some are invested and some want more information and how to share it with the family because our model is to notify the primary care at the same time we're notifying specialists, and we ask the primary care to talk to the family as our preferred method of communication.

So we have some who are very invested, some who don't want anything to do with it. Can't wait to have that child evaluated by someone else.

But we've also invested a lot of energy in outreach and education. We've done tons of scannings. We do our own internal scanning. We have outreach educators who record our current situation and go out and help with that.

And one of the things that we are trying to do is just to integrate lab and follow-up for our educational efforts. And that's bearing some fruition as well, because previously there's been such divergence. But we've utilized all of the resources we can.

And to Joan's point, we do use some Title V funding for some of the newborn screening educational efforts and to support some aspects of the follow-up on newborn screening as well. But again, that's a state decision.

So I think that there's no quick answer. The AAP supports newborn screening. The education on the ground is going to have to be very diverse. Some folks have tried to integrate it into the EMR's, but there's a popup, and some systems have done that related to newborn screening. With more

information, it either takes them to UpToDate or wherever it's going to take them to. And so I think we need to come up with some diverse methods of education.

And the other thing also, the plank for the education, is that traditionally in newborn screenings, printed brochures did educational things both for families as well as their providers. You know, the printed brochures are not where most people are at now. You know, we've changed. Methods of communication have changed.

So, you know, I think we need to start thinking about how we approach folks where they are with the education part of this because we're clearly not getting through to a lot of folks.

So I'm going to stop there because I could go on forever. Thank you very much.

MELISSA RASPA: Yeah. I just want one final comment if I have time, Dr. Powell.

CYNTHIA POWELL: Go ahead.

MELISSA RASPA: I think if the evaluation tells us anything, it's that there's no silver

bullet for any of these goals, and there's no one-size-fits-all model that's going to work for all states or all stakeholders. I think their point, Debra, around stating different options, different methods is really what's needed, but all with the same purpose in mind.

Because without that, I feel like it's kind of dead in the water. You just can't assume you're going to create a brochure and it's going to work, right? So there really had to be some creative thinking and really different layers of strategies to help make sure that all of that information is getting to the people, the right people at the right time.

CYNTHIA POWELL: And on the prenatal side of things, I hope it's not a reflection of how they feel about this. But despite having a place at the table among the organizational representatives, we've had no one from the OB/GYN Association attend any of our meetings for at least the last year. So hopefully we can find someone out there from that community who can

truly engage in our Committee meetings, at the least.

So, time to rest, but I want to thank you for this very informative presentation. I was glad to see that several of the things highlighted in the information you received in this project the Committee has also been hearing about over the last few years. So hopefully we can continue to work together on these issues.

I'm now going to turn things over to Mia Morrison, who will talk about our workgroup meetings that will begin at 3:00 p.m. Eastern time.

Mia.

MIA MORRISON: Thanks, Dr. Powell. I just wanted to hopefully review instructions for accessing the workgroup meetings. So you can go to achdncmeetings.org/registration/. And members of the public, you're welcome to attend, but we ask that you remain in listen-only mode unless called upon by the chair or co-chair.

If you have any technical difficulties

accessing the webinar meetings, please contact me at achdnc@hrsa.gov. Thank you.

ADJOURNMENT

CYNTHIA POWELL: So this concludes day one of the August ACHDNC meeting. Thank you to the Committee Members, organizational representatives, and members of the public for attending. And we'll reconvene tomorrow at 10:00 a.m. Eastern time.

Thank you.

(Whereupon, the meeting concluded.)