THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

WEBINAR

Thursday, November 14th, 2024

10:00 AM – 3:50 PM Eastern Time

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COMMITTEE MEMBERS:

Ned Calonge, MD, MPH (Chairperson)
Associate Dean for Public Health Practice
Colorado School of Public Health

Michele Caggana, ScD
Deputy Director, Division of Genetics
New York Department of Health

Janine Cody, PhD
Professor, Department of Pediatrics
Director, Chromosome 18 Clinical Research Center
Founder and President
The Chromosome 18 Registry & Research Society

COMMITTEE MEMBERS
(CONTINUED)

M. Christine Dorley. PhD, MS, MT (ASCP)
Division Chief, Newborn & Childhood Screening
Maryland Department of Health – Laboratory
Administration

Ashutosh Lal, MD
Professor of Clinical Pediatrics
University of California San Francisco (UCSF) School of
Medicine

EX - OFFICIO MEMBERS

Agency for Healthcare Research & Quality
Robyn Sagatov, PhD, MHS, RDN
Senior Advisor
Child Health and Quality Improvement

EX-OFFICIO MEMBERS
(CONTINUED)

Centers for Disease Control and Prevention

Carla Cuthbert, PhD

Chief, Newborn Screening and Molecular Biology Branch

Division of Laboratory Sciences

National Center for Environmental Health

Food and Drug Administration

Paula Caposino, PhD

Acting Deputy Director, Division of Chemistry and Toxicology Devices

Office of In Vitro Diagnostics

EX-OFFICIO MEMBERS
(CONTINUED)

Health Resources & Services Administration

Jeff Brosco, MD

Director

Division of Services for Children with

Special Health Needs

Maternal and Child Health Bureau

National Institute of Health

Diana W. Bianchi, MD

Director

Eunice Kennedy Shriver National Institute of Child

Health and Human Development

DESIGNATED FEDERAL OFFICER

CDR Leticia Manning, MPH

Health Resources and Services Administration

Genetic Services Branch

Maternal and Child Health Bureau

ORGANIZATIONAL REPRESENTATIVES

American Academy of Family Physicians

Robert Ostrander, MD

Valley View Family Practice

American Academy of Pediatrics

Debra Freedenberg, MD, PhD

Medical Genetics Consultant

ORGANIZATIONAL REPRESENTATIVES
(Continued)

American College of Medical Genetics & Genomics

Cynthia Powell, MD

Professor of Pediatrics and Genetics

Director, Medical Genetics Residency Program

Division of Pediatric Genetics and Metabolism

The University of North Carolina at Chapel Hill

American College of Obstetricians & Gynecologists

Steven J. Ralston, MD, MPH

Chair, OB/GYN

Pennsylvania Hospital

Association of Maternal & Child Health Programs

Sabra Anckner, RN, MSN

Acting Organizational Representative

Associate Director, Clinical & Community Collaboration

ORGANIZATIONAL REPRESENTATIVES
(Continued)

Association of Public Health Laboratories

Susan M. Tanksley, PhD

Manager, Laboratory Operations Unit Texas Department of State Health Services

Association of State & Territorial Health

Scott M. Shone, PhD, HCLD(ABB)

Director, North Carolina State Laboratory of Public Health

ORGANIZATIONAL REPRESENTATIVES
(Continued)

Association of Women's Health, Obstetric & Neonatal Nurses

Shakira Henderson, PhD, DNP
Dean, College of Nursing – Chief Administrative Officer, UF College of Nursing
Associate Vice President for Nursing Education, Practice and Research – System Chief Nurse Executive, UF Health
University of Florida

Child Neurology Society

Margie Ream, MD, PhD
Associate Professor
Director, Leukodystrophy Care Clinic
Director, Child Neurology Residency Program
Nationwide Children’s Hospital, Division of Neurology

ORGANIZATIONAL REPRESENTATIVES
(Continued)

Department of Defense

Jacob Hogue, MD

Lieutenant Colonel, Medical Corps, U.S. Army

Chief, Genetics, Madigan Army Medical Center

Genetic Alliance

Natasha Bonhomme

Vice President of Strategic Development

March of Dimes

Siobhan Dolan, MD, MPH, MBA

Professor and Vice-Chair, Genetics and Geonomics

Department of Obstetrics, Gynecology, and Reproductive Science

Icahn School of Medicine at Mount Sinai

ORGANIZATIONAL REPRESENTATIVES
(Continued)

National Society of Genetic Counselors

Amy Gaviglio, MS, CGC

Founder and CEO

Connetics Consulting LLC

Society for Inherited Metabolic Disorders

Susan A. Berry, MD

Professor, Division of Genetics and Metabolism

Department of Pediatrics

University of Minnesota

P R O C E E D I N G S

10:01 a.m.

Welcome, Roll Call, Opening Remarks, and Committee Business

CHAIR CALONGE: Good morning everyone. I'm Ned Calonge, Chair of the Advisory Committee on Heritable Disorders in Newborns and Children, and I'm happy to welcome you all to the November Advisory Committee on Heritable Disorders in Newborns and Children. This is our November 2024 meeting, and our final meeting for this year.

I have some opening remarks, but first I'd like to turn things over to Leticia Manning for roll call and additional information on this FACA meeting. Leticia?

COMMANDER MANNING: Thank you. Good morning everyone. So I'm going to start with the roll call for the Committee Members. From the Agency for Healthcare Research and Quality Robyn Sagatov.

DR. SAGATOV: Present.

COMMANDER MANNING: Michele Caggana?

DR. CAGGANA: Good morning. Here.

COMMANDER MANNING: Ned Calonge?

CHAIRMAN CALONGE: I'm here.

COMMANDER MANNING: From the Centers for Disease Control and Prevention Carla Cuthbert?

DR. CUTHBERT: I'm here. Good morning.

COMMANDER MANNING: Good morning. Janine Cody? Christine Dorley?

DR. DORLEY: Here.

COMMANDER MANNING: From the Food and Drug Administration Paula Caposino?

DR. CAPOSINO: Here.

COMMANDER MANNING: From the Health Resources and Services Administration Jeff Brosco?

DR. BROSCO: Here.

COMMANDER MANNING: Ash Lal?

DR. LAL: Here.

COMMANDER MANNING: From the National Institute of Health Melissa Parisi.

DR. PARISI: Here.

COMMANDER MANNING: And now I'll move to the organizational representatives. From the American Academy of Family Physicians, Robert Ostrander.

DR. OSTRANDER: Here.

COMMANDER MANNING: From the American Academy of Pediatrics, Debra Freedenberg?

DR. FREEDENBERG: Here.

COMMANDER MANNING: And the American College of Medical Genetics, Cindy Powell?

DR. POWELL: Here.

COMMANDER MANNING: From the American College of Obstetricians and Gynecologists, Steven Ralston, or is there another delegate from another representative from the American College of Obstetricians? No. Okay. From the Association of Maternal and Child Health Programs, do we have an org rep?

From the Association of Public Health Laboratories, Susan Tanksley?

DR. TANKSLEY: Here.

COMMANDER MANNING: From the Association of State and Territorial Health, Scott Shone?

DR. SHONE: Here.

COMMANDER MANNING: From the Association of Woman's Health Obstetric and Neonatal Nurses, Shakira Henderson?

MS. HENDERSON: Here, good morning.

COMMANDER MANNING: From the Child Neurology Society, Margie Ream?

DR. REAM Here.

COMMANDER MANNING: From the Department of Defense, Jacob Hogue? From the Genetic Alliance Natasha Bonhomme?

MS. BONHOMME: Good morning, here.

COMMANDER MANNING: The March of Dimes Siobhan Dolan?

MS. DOLAN: Here.

COMMANDER MANNING: From the National Society of Genetic Counselors Amy Gaviglio?

DR. GAVIGLIO: Here, and Happy Genetic Counselor Awareness Day to all who celebrate.

COMMANDER MANNING: Thank you, Amy. And from the Society for Inherited Metabolic Disorders Sue Berry.

DR. BERRY: Here. Nice to see you all.

COMMANDER MANNING: Nice to see you too. So, now I'm just going to move on to some general information about the Federal Advisory Committees.

All Committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register, and/or are announced at the opening of the meeting.

For the November meeting we posted it in the Federal Register notice. We said that there would be a public comment period, and that public comment period

will be after lunch today. Only with advance approval of the Chair or DFO, may public participants question Committee Members or other presenters.

Public participants may submit written statements. We did not receive any, but that does not prohibit you from submitting a written statement. As a reminder, it is stated in 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.

And any further public participation will be solely at the discretion of the Chair, and the Designated Federal Officer. As a reminder for ethics and conflict of interest I will remind all Committee Members that you must recuse yourself from participation in all matters likely to affect the financial interest 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.

There is no vote scheduled for today, so just I'm making sure all Committee Members are aware of that. And for our webinar instructions, members of the public, audio will come through your computer speakers. There's also a call-in option for Committee Members and organizational representatives, audio will come through your computer, you can speak through your computer if you need to call in using the phone line, you can do that also.

Please speak clearly, and remember to state your name to ensure proper recording for the Committee transcription minutes. In order to facilitate discussion please remember to raise your hand feature when wanting to make any comments during the Committee discussion. If you're having technical difficulties, please email me, and we will identify a work around.

And those are you also have the close

caption option at the bottom of the Zoom, and that is for Committee Members and organizational representatives, as well as the general public. And now, I'm going to turn it back over to Ned. Oh, I'm sorry. I have one more announcement.

Our 2025 Advisory Committee Meeting Schedule is already posted on our website. The next meeting will be February the 13th through the 14th. We also have meetings on May 9th, August 14th through the 15th, and November the 13th through the 14th. We will update the website with information regarding whether the meeting is in person or virtual, so please stay tuned.

Okay. Now, I believe I'm turning it back over to Ned. Thank you.

CHAIR CALONGE: Thanks Leticia. And again, welcome everyone. I wanted to start out just taking an opportunity to acknowledge the devastation caused by Hurricane Helene and Hurricane Milton in our southeastern states. I know many of the state public

health laboratories and other public health departments are continuing their recovery efforts.

I personally, and on behalf of the Committee, want to thank you all for your dedication and resilience in assuring all newborn babies continue to be screened in your states in order to receive timely diagnosis and care. You're in our thoughts, and we appreciate everything that you're doing to move forward.

Can I have the slide on APHL please? I just wanted to also provide a huge thanks, as well as congratulations APHL for hosting a very successful newborn screening symposium in Omaha, Nebraska last month. While I was unable to attend, I heard the meeting was fantastic, and with the robust participation for various newborn screening stakeholders, including families and people with lived experience who have been directly impacted by state newborn screening programs.

Their participation in meetings, conferences, and symposiums, as well as in other venues, is

invaluable, and provides all of us opportunities as well as other public health officials to directly engage with the populations that we serve. Thanks again, APHL for providing the opportunity for this to happen. Can I have the next slide please?

In previous meetings I think I made you aware of the National Academy of Science of Engineering and Medicine study examining the current landscape of newborn screening systems and processes. Over the past couple of months NASEM has had several information gathering sessions for people who are impacted by, and interested in newborn screening programs in the U.S., including families with children, the rare disease community, public health professions, clinical care providers, health care administrators and health care payers.

The ACHDNC also shared information with the National Academies to inform the study. The study has transitioned from that open information gathering into

Committee analysis and writing. After the Committee generates the draft report, it will undergo a rigorous process that excludes sorry, that includes a review from a set of external reviewers.

Using input from this panel of reviewers the Committee will finalize the report. I will tell you, having participated in those review sessions, this is more rigorous than peer review for journal publications. There's a lot of different reviewers who are able to provide expert guidance to inform the Committee in the final product.

The National Academies plans to release the report in late August of next year. We will look to the National Academies in 2025 to share with the Committee their findings. For more information, you can go to the webpage, which I think you can get to with the QR Code.

I don't know if I have the next slide or not. Okay. You can just pause there. As you're aware, the Committee has fully implemented a preliminary nomination

process to ensure nominators have basic information required to complete a full information package. The process allows for the nomination and prioritization workgroup to provide timely information to the nominators prior to them completing the thorough, full nomination package.

In August, the Committee received a preliminary nomination for Gaucher. And in September, the Committee received a preliminary nomination for acid sphingomyelinase deficiency, or ASMD. I provided a letter to both nominators detailing the review from the Committee's Nomination Prioritization Workgroup, and Leticia and I hope to meet with the nominators in the near future to answer questions and provide additional technical assistance.

I also wanted to update you on the ACHDNC charter. Some of you may be aware the charter was set to expire this month. The Committee's charter was approved by Health and Human Services last month, and

with the same objectives and scope of activities that's defined under the previous charter. We are all excited that the charter can continue to support the Committee in its charge of advising the Secretary of HHS on aspects of newborn and childhood screening for heritable disorders.

You can access the newly approved charter on the Committee website on the "About the Committee," page at Heritable Disorders-About the Committee online HRSA. The website I believe for ACHDNC is pretty easy to navigate. I always find it a rich source of information that I'm trying to find.

You might have recognized this slide from previous meetings. We updated this earlier in the last year and this year, the updates were to try to ensure that the matrix reflects how we're actually making decisions, and have over the last ten years or more. During the last meeting we formally voted to adopt the revised decision matrix, and since that time I've worked

with HRSA and others to create definitions and descriptive language for the revised decision matrix.

This information was included in your briefing book, and although we're not going to have a vote at this meeting, I encourage you to review these definitions and descriptions carefully, provide us feedback as well because this is what ACHDNC will use to make recommendations to the Secretary on whether to recommend the addition of a condition to the RUSP.

The descriptions and definitions will also be available on our website. Next slide. Amazingly, we're reaching our 20th anniversary, and the February 13th and 14th meeting will be our opportunity to recognize the anniversary. We're planning some special presentations to commemorate what we feel is the momentous occasion, and I'll ask you to keep your eye out for information regarding the meeting and our anniversary as it grows nearer.

The next part of Committee business is to

recognize that our membership is, as it does, transitioning once again, and we would like to take a moment to recognize a couple valuable Members invaluable Members, of the Committee who are rotating off.

I'm going to start with Jennifer Kwon. Can I have the next slide please? Jennifer couldn't be with us today, but I just wanted to say a few words in recognizing her service. We weren't able to properly thank Dr. Kwon and Chanika Phornphutkul, for their service last meeting, but their term ended in July, and I wanted to just talk about what Jennifer did during her time with us.

She joined the Committee in January of 2022, and we made her hit the ground running. She served on the ACHDNC Follow-up and Treatment Workgroup, the Nomination and Prioritization Workgroup, and the Evidence Review Group for Krabbe.

She was and is always extremely thoughtful in

her responses and input, and her expertise in pediatric neurology was invaluable to us doing our work at the highest levels. We appreciate her dedication; appreciate the time she invested in this Committee. I appreciate having a relationship with her where I could experience the breadth of her knowledge and her thoughtful input, and I want to recognize the impact she made on newborn screening.

If you have opportunity in future meetings, or in other settings, I hope you take the opportunity to thank Jennifer. Our second person rotating off in last July is Chanika Phornphutkul. And Chanika has joined us this morning, and Chanika, I wonder if I could just give you the opportunity to say a few words.

DR. PHORNPHUTKUL: Well, thank you very much. It has been an honor to be a part of this Committee, and I wish the Committee best of luck for many more conditions that we will continue. I learned a lot, and it's been really great, and thank you everyone.

CHAIR CALONGE: Thank you. I'm pointing out that Chanika also joined the Committee in January of 2022. She served on the ACHDNC Follow-up and Treatment Workgroup, and more recently served as the Committee Liaison to the Evidence Review Group for Metachromatic Leukodystrophy and Duchenne's Muscular Dystrophy.

She has extensive expertise in state newborn screening, endocrinology and treatment of rare diseases in pediatric patients, and has been just a tremendous asset to the community. We'll have a hard time replacing. Thanks so much for your service, Chanika.

DR. PHORNPHUTKUL: You're welcome.

CHAIR CALONGE: The August 2024 meeting summary was included in the materials. I want to thank the Committee Members and Organizational reps for reviewing the summary, and providing input for changes. There was one edit in the meeting summary, and Leticia sent a revised meeting summary I think a couple days ago. I would ask are there any other corrections to the

meeting summary before we vote to approve?

Seeing none, can I have a motion to approve?

DR. LAL: I put forward the motion to approve.

CHAIR CALONGE: Thanks, Ash Lal, and could I have a second?

DR. CODY: I'll second, Jannine Cody.

CHAIR CALONGE: Thank you, Jannine. I'll turn things over to Leticia for the roll call vote.

COMMANDER MANNING: Sorry, Ned, I already did it. Sorry about that.

CHAIR CALONGE: So

COMMANDER MANNING: The roll call, oh I'm sorry.

CHAIR CALONGE: The vote, I'm sorry, yeah.

COMMANDER MANNING: Yes, I'm sorry. I'll go back to that.

CHAIR CALONGE: Just the Members.

COMMANDER MANNING: Noted. From the Agency

for Healthcare Research and Quality Robyn Sagatov?

DR. SAGATOV: Yes.

COMMANDER MANNING: Michele Caggana?

DR. CAGGANA: I approve.

COMMANDER MANNING: Ned Calonge?

CHAIR CALONGE: Yes.

COMMANDER MANNING: Carla Cuthbert?

DR. CUTHBERT: Yes, I approve.

COMMANDER MANNING: Jannine Cody?

DR. CODY: I approve.

COMMANDER MANNING: Christine Dorley?

DR. DORLEY: Approve.

COMMANDER MANNING: Paula Caposino?

DR. CAPOSINO: Yes.

COMMANDER MANNING: Jeff Brosco?

DR. BROSCO: Yes.

COMMANDER MANNING: Ash Lal?

DR. LAL: Yes.

COMMANDER MANNING: And Melissa Parisi?

DR. PARISI: Yes.

COMMANDER MANNING: Thank you.

CHAIR CALONGE: Thank you so much. The meeting notes are approved unanimously, and we'll move on. Just to remind you of what we're doing today, the morning we're going to begin with an overview of the Newborn Screening Information Center Health Information Center. So, we're going to transition to a panel presentation on Research Funding Opportunities to Document Lived Experience of Patients and Families.

We'll take a break for lunch, and resume with public comments. Then, we'll have a project update on the family outcomes of the newborn screening project, and we'll get an update from the Evidence Review Group on the Metachromatic Leukodystrophy evidence review.

We're going to close the information in the meeting today with two additional presentations on Laboratory Developed Tests, and Higher Tier Testing.

Newborn Screening Health Information Center Overview

CHAIR CALONGE: So, I want to transition now to the presentation from the Newborn Screening Health Information Center.

The Newborn Screening Saves Lives. Legislation requires HRSA to maintain a clearinghouse of newborn screening information. The Newborn Screening Information Center or NBSIC provides up to date information and resources about newborn screening to both parents and health care providers.

To discuss and present today is Molly Lynch, who is the Director of the Audience Engagement Research Program within RTI International's Communication Practice Area. She currently serves as the RTI Project Director for the HRSA funded projects, for constant development for the Newborn Screening Information Center.

Molly has over ten years of experience engaging families and health care providers to develop

and evaluate newborn screening educational resources, and I would like to turn things over to you, Molly, and thanks for joining us.

MS. LYNCH: Thank you so much. I'll get my presentation up here. Great, wonderful. Okay. Well, good morning to everyone, and thank you so much for that introduction. Again, my name is Molly Lynch, and I'm with RTI International. We are a nonprofit research institute located in North Carolina, and we're the contractor as we were introduced, who’s currently managing the content for the Newborn screening Information Center.

So, I'm very pleased to be here to provide an overview of the site this morning. Okay. Before I get into the site, I just wanted to take a moment to introduce the RTI team. We are a multi-disciplinary team, and we're able to draw from several disciplines to ensure that we develop content for the site that is not only accurate, but also content that is engaging, and

resonates with the site's intended audiences, which is primarily parents and caregivers, as well as health care providers and other public health professionals.

So, you can see that we have a bench of newborn screening experts, including genetic counselors, who review all of our content, including the conditions pages regularly, and I'll show you those condition pages in a moment. But also, we have a communication science team and a digital and content strategy team, and that's really to ensure that the web content is accessible, and user centered, and follows a strategy to reach these audiences.

Okay. So now onto the site. The Newborn Screening Information Center was launched in 2020 as part of the legislation from the Newborn Screening Saves Lives Reauthorization Act, to maintain that clearinghouse of information about newborn screening.

Previously, the clearing house was maintained on baby's first test, but the reauthorization of the

legislation required the site to be hosted on the HRSA.gov site, and HRSA worked with the National Institute for Children's Health Quality, and expecting health to build the information center, starting in 2020.

And then we were contracted by HRSA last fall, so we've been on this project about a year to maintain and develop new content for the site, and we are just very excited to work with HRSA on this project.

Okay. So, now without further ado, I will actually go to the site, and give a brief tour. Let me navigate there. So, the URL for the site is Newborn Screening.HRSA.gov. I hope everybody will remember that, and come back to the site frequently, but this is the home page for the site, and it starts in this yellow box by giving an overview of what an intended user might find on the site.

And then there are six tiles below that helps people navigate to important information about newborn

screening. So, I'll go through a few of these tiles, and we'll check out kind of key aspects of the site. So these first two tiles are really more basic information about newborn screening and the newborn screening process, so I will click on this one here to take you to the newborn screening process page.

This is of course a very critical piece of information that new parents and expecting parents are looking for. This page is actually undergoing some transformations and enhancements, and that will roll out later this year, but currently the page is organized by some key questions here. When does newborn screening happen? Where does it happen? How does it happen, as well as some questions to ask in how newborn screening is different across each state and territory.

So, this is one long super page with a lot of important information. So, I will go back to the home page. Another key aspect is newborn screening in your state or territory, so this is another key aspect of the

site as we navigate here. You'll see an alphabetical listing of all state and territorial newborn screening programs, and I'll show you what each state's page looks like.

I will select North Carolina because that's where I'm calling in from today, but each page follows a very similar structure here, so you can see at the top is the name of the state, and then begins an alphabetical listing of both the core and secondary conditions screens for in that state, and we are in contact with state newborn screening programs to make sure that this list stays up to date.

At the bottom you'll find the contacts for the state newborn screening program, as well as the early hearing detection and intervention program, so that this information is accessible, as well as links to additional resources. So, another key aspect of the site is you can see there are hyperlinks under each condition, so if you wanted to know more about a

specific condition, such as cystic fibrosis, you would click here.

And then this is another kind of really rich portion of the site where we provide a page for each condition, so this as you can see, this is for cystic fibrosis. Again, each condition follows a similar structure, so you begin with a general condition information where there's information about birth prevalence and the screening finding, as well as other names that the condition may go by.

And then you, as you navigate down the page, there's a description of the condition, kind of background information, as well as getting into then more specific information about newborn screening and follow-up for that particular condition. So, what does screening for cystic fibrosis look like?

They talk about that, and then what happens if there's an out-of-range screening result? Under condition details there is information here on the signs

and symptoms, the cause, as well as inheritance and family concerns. And then the page wraps up with treatment and management information, as well as related resources that are really specific to that condition.

I wanted to know, as I mentioned earlier, this is a these are a set of pages that get reviewed quarterly by our team of genetic counselors to ensure that any clinical updates are reflected on a quarterly basis. The other aspect I wanted to show on this page is that if you click on this Espanol button up here.

Every page has the option of being translated into Spanish, and we have a Spanish content team that also reviews these, so this is not an AI translation, we have real people with genetic counselor backgrounds who are reviewing this, the pages in Spanish as well. You'll see that, and every page on the site is available in Spanish.

Okay. We'll go back to English for the duration of the tour here. The next thing I wanted to

show was that we do have a glossary. The site does have a glossary located right here at the top, and if you find, let's see, a term on here that may not be known to from a general audience, such as pancreatic enzymes, if you click on that it will take you, and there's a plain language definition for all of these terms that may be sort of more medical or technical jargon available in plain language.

And the glossary page, if you just want to peruse the glossary is here, and it's an alphabetical listing of all of these terms, but they are hyperlinked throughout the site, so that anybody reading the site would be able to find a definition of that term. Okay. All right.

I think I'll wrap up with the newborn screening for providers page here. So, while the rest of the site is really meant for and accessible for parents, caregivers, and kind of anybody from the general public, or professional audience, this page is

specific to providers.

We do intend to kind of build out this page a bit more this year, that is in the plans, but I did want to let everyone know about this page specifically within the site, and then there's a new resource that we've been working on over the last year that has just hot off the press, and has just recently been posted, and it's the communicating out of range newborn screening results to parents and families.

So, this is really a guide specific to providers that they can use for those conversations that can be quite difficult, and potentially emotional, and it's really a resource for providers to use in that context. So, I'll just do a brief demo of this resource. So, it is organized around what we call the four C's, so kind of a shorthand to remind providers what the key aspects of communication around this topic area are.

So, clarity, compassion, continuity of care

and connection, and then within each of those C's there are some kind of guidance about what the key information needs that parents might have at that time, as well as conversation starters for kind of each of these four buckets of information. We were able to test this with both health care providers and parents last year, and reflected any feedback from them, so that this is a tested resource that we have made sure resonates with health care providers who might be using this tool, so, that is available now on the site.

Okay. Well, that's the overview, and I'll go back to the presentation now, and just run through a few more slides about what we've done this year, and what we hope to do on the next year. Okay. So, our goals as the contractor for managing content on the site are really four-fold.

The first is we really do want to continue to engage with state and territorial newborn screening programs because that is so important to keep the site

up to date and keep those state panels accurate with any conditions that may have been added, or removed on a quarterly basis.

Similarly, we also will continue to conduct expert review of those condition pages, and add new condition pages as needed. We also use insights from website audiences, so parents and caregivers, and health care providers, to develop new content and website enhancements that will really resonate with these audiences.

And finally, we just want to create a resource that is out there without getting into the hands of people who really need this information, so we also have a goal to promote the site to parents, health care providers, and other key audiences.

All right. I'll talk a little bit, as I mentioned, about what we did this past year to enhance the site, as well as plans for future enhancements. So, one thing we worked on last year was to redesign the

home page. Previously it had four links to take you to key pieces of information. We've expanded that to six to include results and follow-up information, as well as the resources pages, just hearing from parents that those were really important pieces of information to be able to locate quite quickly.

So, we've done a bit of that home page redesign, as you could see on the overview. Okay. As I mentioned, we do have a lot of communication and science background on our projects, so one of the key aspects we looked for was to make sure that when you go to a page the main message is highlighted. That's just important for audiences to be able to take away that key information, even if they're just glancing at a page.

So, we have developed or highlighted main messages on each page to let that website user know what they are expected to learn or do on the page, or you know, potentially a key takeaway message that they could remember after visiting the site. We've also added some

visual enhancements, so we've added some photography to the site, photographs and visuals are of course just help break up the text and make the site more engaging, so we worked to add those to these key pages last year.

We also reorganized the resources page, so that the more parent centric resources came first. There's a long list of different types of resource pages on this page, and we wanted parents in particular, if they were you know, if they were looking for resources, that they could find those easily. So, the support and advocacy organizations are now at the top of the page.

As I mentioned, and I'm sure through the website we also have this out-of-range communication guide for providers, and we're really excited that this is now posted, and this is live. We've been at some conferences over the past month and kind of promoting this resource that we're really excited that it is now available to the public.

It will also be available in Spanish in the

next month or so to be posted on the site. Okay. We also have some plans for future enhancements. These will be available in both English and Spanish, so there will be some new content on the road to the RUSP, so there will be some text and visuals and graphics that really describe that process for adding conditions to the RUSP, so that will be coming later this year.

We will also be adding some just additional parent friendly newborn screening resources through webpages, infographics and other content so that the newborn screening process is really accessible to parents. They can look at a visual representation that is also in plain language, and easily understand the process.

And then finally, as I mentioned, we will be enhancing the provider page, so we've added that new resource, but we're excited to kind of expand out that content a bit more and make that page really useful for providers.

All right. And as I mentioned, we do want to promote the site to make sure this information gets into the hands of the people who need it, so we do submit abstracts, at least three per year, and recently we just presented at APHA, APHL, and the American Society of Human Genetics, so that happened in the past month.

We will also continue to develop content partnerships, so what that means is really having a partnership with other key organizations in this community, such as state newborn screening program websites, and other professional and advocacy organizations, so that we could link the Newborn Screening Information Center, so if audiences are on that site, they could see a description of what the NBSIC is, and then link back to our site.

And then we will also leverage the social media around key observances, so we ran kind of a pilot, a social media campaign for Newborn Screening Awareness Month in September, and had some really nice results

from that, so we will continue running social media ads throughout the year around some key observances.

We will also implement some Google search ads, such as our paid ads that come up when somebody is searching about newborn screening, and that will go to the top and help direct people to the site. And then we do have to have a larger, as I mentioned, it was sort of a pilot campaign this past September still looking for a bit more social media presence in the next September Newborn Screening Awareness Month.

So, I will wrap up here, and I'd be happy to answer any questions about the site. This is a QR Code to take you there, this is also the URL NewbornScreening.HRSA.gov, and we hope you'll visit and review peruse the site, so thank you so much.

Committee Discussion

CHAIR CALONGE: Thank you, Molly. That was super. Well, I'll open the floor for discussion

starting with Committee Members, and then moving on to our Organizational reps. I did want to perhaps start with one of the recommendations that you probably already know, but as you think about promotion, I hope you think about promoting to those who would use the information to relay information back to patients and their families.

I thinking specifically of pediatricians, family physicians, OB/GYNs, and advanced practice nurses who provide that care as well, so that you know, all of those groups have annual meetings with scientific presentations, and understanding this resource is out there, even if you're not going to memorize the conditions, knowing where to go when something pops out when you get something that's positively useful.

And my question is when you say gather insights from different audiences, is that passive or active in terms of, you know, getting information to make the website better?

MS. LYNCH: Yes. Thank you so much for both of those points. I think we've been talking a bit internally with our HRSA colleagues about how to reach those providers, so we'll definitely be integrating that into our promotion plan for this year. And then yes, thank you for the question about user insights. We actually have a separate contract that's around evaluating the site.

And so, through that contract we are able to more directly engage with our intended audiences through usability interviews, where we recruit members of the audience, and we have them look at the site, and we've been able to gather some really great insights from both parents and health care providers about what their information needs are, and how we can best reflect that in the site.

CHAIR CALONGE: I appreciate that. Thanks. Christine?

DR. DORLEY: Thank you for a really good

presentation, Ms. Lynch. My question or comment, I know that this body at some point has to make a decision regarding counting conditions because of the seemingly disparity between states.

But in the interim, are there any plans to kind of minimize some of that confusion, or this pseudo disparity that exists by perhaps separating out the target conditions, or the core conditions from the secondary targets based on how states are indicating that, for instance in Maryland we say we screen 62, and I notice North Carolina has 60 disorders that they're screening for.

Is there any kind of plan in the interim to try to help minimize some of that confusion?

MS. LYNCH: What a great question, and this is definitely something that has been on our radar. We have conducted some listening sessions with state newborn screening programs last spring, and this definitely came up, so it is something that is

definitely on our kind of just we're definitely thinking about it in consultation with our HRSA colleagues.

As I mentioned, we did some usability interview testing on the separate evaluation contract, and through that we were actually able to test some different iterations of what the page could look like with core versus secondary conditions separated out. So, we do have some data around that from what users would appreciate.

I don't think we have any firm decision right now, but we are also extremely interested in following the guidance of this Committee along with it, so it's definitely a big issue. We have it on the radar, but the plan is not final for how we will address that I could say at this moment.

CHAIR CALONGE: Thanks. Ash?

DR. LAL: Thank you. So my comment is I think is follow-up on Ned's comment that is there a link out, for inclusion of treatment sites for rare disorders

that are easily accessible, because that sometimes is one of the initial questions that comes up, maybe even at the level of the primary care providers?

So, is there is that within the scope of this site to have an active listing, or maybe a link out is more appropriate, how do you think that should be?

MS. LYNCH: And I'm sorry, I'm not sure I understand the question.

DR. LAL: So, for most of the rare disorders there are a limited number of specialty treatment centers, especially for new therapies like the gene therapies for example. They initially can only be set up in a limited number of centers around the country. Every state may not have a designated center within the state, maybe in the neighboring state or maybe something in the region that...

How is that information? That's what I wanted to ask, is that information a part of the scope of this website, or could you provide a link to the

provider section to where that information can be found?

MS. LYNCH: So, that's a great suggestion. I don't think it's currently a part of the scope, but you know, this is wonderful feedback that we would definitely look into and discuss. It sounds like a very important set of resources to link out to on the provider page, so I really appreciate that.

CHAIR CALONGE: Thanks. Cindy?

MS. POWELL: Thank you. Hi. Cindy Powell, ACMG Org rep. Thank you, Molly, for the presentation, and great work on that website. I know you mentioned you're still developing the provider portion, but I did wonder if you will be able to link to the ACMG Act sheets that do give, you know, some specific information about the disorders, both those on the RUSP, and other rare diseases.

MS. LYNCH: Yes, thank you Cindy, that is definitely something also on our radar, and we'll be discussing with our HRSA colleagues, you know, the best

place to put those, and if they belong on the Newborn Screening Information Center, or we can link to them specifically, so definitely something worth discussing.

MS. POWELL: Thank you.

CHAIR CALONGE: And Amy?

DR. GAVIGLIO: Yeah, thank you. So, Amy Gaviglio, Org rep, NSGC, and I'm saying this as someone who has been involved in this work since it was really NICHQ who first worked on the site with Expecting Health Babies First Test is a subcontract, and now with RTI, but I am getting a bit concerned about the diffusion and redundancy of some of the educational efforts because I think it's becoming difficult for programs to know kind of where to send families and providers to.

And I think, particularly if I look at obviously, I believe that the communication guide is very important, but it's very similar to a document we created with the Education and Training Workgroup, and we worked hard to link that to the Act sheet, and share

it with programs.

And so, I think as we create similar documents, we're going to have to really do an environmental scan of where those have been linked to. Do we continue to use the one the initial one that HRSA helped us develop? This new one?

So, I would just overarchingly encourage us to really understand what has already been done, and what has been shown to be effective through evaluative measures, and how we may really need to think more kind of innovatively about different education and engagement opportunities, so we're not just kind of recreating things that we've done in the past, so that's just an overarching comment on education and newborn screening in general.

MS. LYNCH: Yes. Thank you so much, Amy, that is a very well-said remark, and we'll always take that under consideration.

CHAIR CALONGE: Well, great, and thanks

again, Molly, so much. It was a great presentation. The work looked engaging. I appreciate your receptivity to comments, and we look forward to the evolution of the website moving forward. Thanks so much.

Research Funding Opportunities to Document Lived Experience of Patients and Families

CHAIR CALONGE: I'm really excited about moving to the next section, which is Research Funding Opportunities to Document Lived Experiences of Patients and Families. During the last couple of years the Committee has heard through public comments, and other mechanisms of feedback during experiences with parents, patients and families impacted by the newborn screening conditions that are under review by the Committee.

The stories and the experiences that are shared with us have been powerful, and we're always grateful to all the families that have shared, and who will continue to share. The ACHDNC Evidence Review

Group and the Committee are unable to use the information shared during public comments to impact our recommendation, unless it's also included in research, and in our research framework.

So, we've invited various federal agencies and a presenter from the private sector to share funding opportunities research on rare diseases that could include and will include family and/or lived experiences. Now, due to the number of panelists, I'm going to do a real brief introduction of all of the presenters.

I don't want to in any way discount what is an extensive knowledge and experience base of each of the presenters that we're bringing to the table, and I want to thank them for presenting as well. In order, we're going to start with Dr. Mike Hu, who parented two children with a rare genetic disorder.

He is the Co-Founder and Treasurer of Project GUARDIAN, a nonprofit organization with a mission of

advancing genomic space newborn screening. Then Dr. Nora McGhee, is the Associate Director in the Clinical Comparative Effectiveness Research program at the Patient Centered Outcomes Research Institute, also known as PCORI. She is also the staff co lead for the PCORI Rare Disease Advisory Panel.

Our own Robyn Sagatov, the Ex Officio for AHRQ is the Senior Advisor for Children's Health in the Division of Priority Population in the Office of Extramural Research, Education and Priority Populations of the Agency for Healthcare Research and Quality, or AHRQ.

Dr. Melissa Parisi, our own, is the Chief of Eunice Kennedy Shriver National Institute of Child Health and Human Development, Intellectual and Developmental Disabilities Branch. She currently oversees NICHD's Eunice Kennedy Shriver Intellectual Development Disabilities Research Center.

And then wrapping us up will be Dr. Catharine

Riley, Lead Health Scientist at the Center for Disease Control and Prevention where she currently leads the project focus on the use of large scale electronic health record data on to study rare conditions and emergency public health issues.

Some years ago, Catharine served as the DFO for this very Committee, and so we're thrilled to see her back. So, given that, I'm going to start with Mike Hu.

DR. HU: Thanks, Dr. Calonge. Thanks for the Committee for inviting me to share with you. I didn't know I was going to be the first presenter, so alternative funding opportunities for newborn screening research. And as Dr. Calonge mentioned, Project GUARDIAN is a nonprofit.

We focus on large scale newborn sequencing research studies, so funding needs are high for us, we've certainly seen our fair share of fundraising challenges, so I hope this can be useful for anyone who

is out there who aspire to newborn screening research in all kinds of capacities. Next slide please.

So, the first one I'm going to tap into is the commercial funding. As most of you probably know, most pharmaceutical companies provide funding to the patient community in various forms, mostly through grants, and they support different causes. I have a screenshot for one of the companies here as an example. In this particular company if you're going to the company tab, and then the given program, you will see they have four different focus areas that the company is looking into, and they have a formal grant portal set up, so you can submit your grant requests.

And all of these have additional information, pretty self-explanatory, so you can get into that, and it's geared towards patient advocacy organizations, but individuals can certainly apply for it as well. Some smaller companies may not have such resources to establish grant channels, so in those, and you know, if

your specific indication is being looked into by a company that is small doesn't have that.

I would suggest the first way the first route to go is to find people in patient advocacy roles in those companies. You can either do a web contact search, or LinkedIn searches are actually very helpful. People in these roles are very connected to the patient community, and they are very responsive, so even if you reach out on LinkedIn as a cold message, they will most likely reply to you.

I have certainly seen a lot of those myself, so I would encourage you to do that. And more importantly, I would say this is probably true for all of the other channels I'm going to talk about, but especially for commercial funding, it is important to identify an internal champion who can understand your calls, understand what you're trying to do, and can advocate for you on your behalf in their internal discussions, and grant reviews, and what not, so

definitely try to do that.

Next slide please. The next channel I'm going to talk about is grants from larger pan-disease advocacy organizations. The likes of Ever Life Foundation and Global Genes, which I put here. There are certainly others as well, and you can see in this example for Ever Life, this is from their website. They do provide tools and resources grants for certain eligibilities, and patient experience data collection efforts.

This is certainly within the scope of what lived experience is about. In addition to funding, they also have a lot of useful resources that might be helpful along the way, so I would definitely suggest reaching out to them, even if you are not looking for funding per se, but they will have experts who can provide some useful guidance, and then most likely some useful resources for the particular research that you might be looking into.

Next slide please. The other big channel is philanthropic foundation grants. You've all probably heard about the likes of Gates Foundation, or Chan Zuckerberg Initiative, which I you know put their grants page here as an example. They can certainly be a great resource, and I want to highlight that every foundation works a little bit different, and they all have their own focus areas.

So, here some homework is certainly needed. You need to probably do a search, and to find the one that matches your mission most closely, and then additionally, private foundations are typically flexible in terms of funding projects that may not even be on their map, if you can find someone to talk to you might understand better how that alignment can be established, and so it's a two way conversation.

Again, an internal champion will be very helpful here, so I will certainly suggest reaching out to some of the foundations that is related to the area

that you want to focus in. Next slide please.

And specifically for lived experiences research, there are some additional opportunities out there. One is what probably every patient advocacy organization is familiar with, which is fundraising. In this case, I think some targeted fundraising efforts can certainly help.

When we talk about lived experiences research, I think it can be in the forms of a case study. It can be in the forms of you know surveys, and interviews. So, in order to design those, if there's no readily available ones, you might need some professional guidance in the form of consultants. There may be some manuscript drafting.

A medical writer might be helpful, and at the end there's general publishing cost. All of those add together as, you know, typically not a huge cost. Maybe in the range of five to ten grand, so a targeted fundraising effort can be very helpful in addressing

that gap.

Another one, which is more hidden, I would really like to thank my colleagues, Amy Gaviglio and the National MPS Society, for identifying these. This is something that we actually used before. Thesis work for programs such as genetic counselors, and graduate programs in the area such as ethics, neuro behavior and development.

We've actually used those before in the MPS 2 nomination through researchers at University of Minnesota for a case report. And so, in this case it can drastically simplify your work because graduate students who need to do thesis work are motivated to work with you on, you know, everything that's related to the research. You just need to provide your lived experience, and round up your thesis community to do the same.

And finally, doing it yourself is not it's a last resort, but it's not as challenging as it might

sound. I think, you know, if you can read a few publications in this area you get an idea of what writing a manuscript is about. If you can search for some surveys, design your own isn't that hard. It's always an option, but I do want to highlight that I thank the Committee and HRSA for the effort looking into this area, and trying to turn lived experiences into evidences that we can use in the review process.

That's a great first step. I do want to caution that I hope this becomes not just another hurdle for the nominators to jump through who already have a huge task of sampling the nomination package, so some systemic improvements for research in this area is needed.

The good news is it's on the horizon. Jeff can tell you more about it if you need to, but there are research centers funded by HRSA that are looking into tool kit development for connecting researchers with applicants. Next slide.

Last, just as an example, the funding mix for our project is pretty much all of the above. If you want to know more, feel free to visit our website, and I'd be happy to talk to you more about it individually. Thank you for the opportunity to speak.

CHAIR CALONGE: Thank you so much, Mike. I'm going to ask Committee Members and our Org Reps to hold your questions to the end, so hopefully you've written little notes, things you'd like to ask Mike, and with that let's move on to Nora. Welcome, Nora.

DR. MCGHEE: Thank you so much. Good morning. Thank you for the opportunity to speak to you today about the Patient Centered Outcomes Research Institute, PCORI, and our funding opportunities relevant to those working in the rare disease space. Next slide.

So, I'm going to spend a few minutes telling you about PCORI, and our funding opportunities, as well as our rare disease portfolio. Next slide. First, a bit about PCORI. Next slide. PCORI is an independent,

nonprofit research organization that seeks to empower patients and others with actionable information about their health and health care choices.

We fund comparative, clinical, effectiveness research, or CER, which compares two or more medical treatments, services or health practices. The findings from these studies help patients and other stakeholders make better informed decisions. Next slide.

So some key features of our funded research and research related projects. We engage patients and other stakeholders throughout the research process, and we expect our awardees to do so as well. We're committed to ensuring that they have a seat at the table throughout the lifecycle of the award, helping to prioritize research topics, design, and conduct the studies, and share the results.

As I said, we fund comparative clinical effectiveness research, CER, and the comparators for our research must have evidence of efficacy or use. Our

funded work focuses on answering questions most important to patients, and those who care for them. We believe patients deserve to know whether some approaches work better than others for certain populations, and caregivers, clinicians, and all of our stakeholders benefit from having better information about different care options.

And finally, our funded work aims to produce evidence that can be applied in real world practice settings, which is often not a focus within health care research. Next slide. We have been requiring engagement in our studies for over ten years now, and we have found that true engagement makes meaningful differences, as it influences study conceptualization, execution, and materials, as well as the way study tasks are carried out.

How engagement itself is designed and practiced, and researcher's understanding of the needs of people and organizations. Engagement not only

benefits patients, whose care may ultimately improve based on study findings, but also benefits research teams, and one way is by helping them refine their research questions, thus enhancing the relevance of their results.

Next slide. We have recently developed new foundational expectations for engagement that I urge you to read through on our website. These lay out the requirements, and provide guidance for engaging patients and other important stakeholders during each stage of the research process.

We also have a wealth of other resources there, some of them developed as part of PCORI awards that I think you will find helpful. Some of the resources include information on measuring what matters, guidance on building effective multi stakeholder research teams, and a research fundamentals course that is very helpful for research partners, and this course is also available in Spanish. Next slide.

At the core of what we do at PCORI are five national priorities for health. These are ambitious, long-term goals that will guide PCORI's funding of patient centered CER, and other initiatives related to engagement, dissemination and implementation, and research infrastructure. I won't read through them, but you can find them on the right-hand side here.

Next slide. PCORI has an interest in research across a range of areas, but we have a particular focus on the topic themes of interest that will inform focused funding opportunities over the next several funding cycles. We have had a long standing legislatively mandated rare disease advisory panel that has affirmed our interest and work on rare diseases.

And our Board has amplified that by confirming addressing rare diseases as a topic theme of interest as you can see here. Next slide. So now I want to give you a sense of the types of PCORI funding opportunities available, any of which might be a

possible avenue for work in rare diseases. Next slide.

So here you can see descriptions of the research funding announcements we will be offering in 2025. Most of these announcements are offered three times each year. The first is our broad, pragmatic studies, or BPS funding opportunity. This opportunity seeks applications on investigator-initiated topics, which include rare disease.

The funding announcement allows three types of award, which can go up to $12,000,000 in direct costs, and last up to five years. The second type is our method funding announcement, which supports work that will ultimately improve the design and conduct of CER. Next, is our science of engagement. This is a multi-year effort to build an actionable evidence base that clearly identifies the methods and approaches that lead to effective engagement in research.

Next, are our topical announcements. These are focused on specific high impact topics aligned to

our topic themes, with the aim to produce evidence that will have a substantial impact on practice and patient outcomes. A recent topical funding announcement was focused on rare diseases, but we expect to make awards for this in the spring.

Next is our PLACER, the Phased Large Awards Comparative Effectiveness Research announcement. This supports large scale, high impact randomized trials in CDR, with risk in achieving their research aims, merits and initial period of testing and refinement to determine their feasibility and viability, and maximize the likelihood of full scale trial success.

These can last up to six and a half years total, and could be up to $22,000,000 in direct costs. I encourage you to visit PCORI.org to review the detailed funding announcements. We also have a dissemination and implementation awards program that I won't have time to describe today. Next slide.

Here you can see information about the

different competitive engagement funding opportunities we offer. The 2024 deadlines have passed, and the 2025 ones have not yet been released, but we do expect them to be in the spring and fall. Most of our engagement awards fall under capacity building. They provide an opportunity for organizations and community groups to build capacity and skills for CER.

The dissemination initiative supports organizations and community groups that have established relationships with end users to disseminate the findings from PCORI funded studies. They can disseminate the PCORI study alone, or as part of a body of evidence that's relevant. The convening support program provides funding for stakeholders to explore critical issues related to CER.

The awardees may also communicate PCORI funded research findings to end users. Next slide. So, now I want to spend a few moments giving you a sense of PCORI's varied rare disease portfolio. Next slide.

We have funded 41 rare disease studies for a combined total of $120,000,000 in research funding. We have also funded over 60 rare disease engagement studies, next slide. You can see here that our rare disease research awards are across a large number of different conditions, most of which you'll see listed here on the right. Several of the awards are cross cutting, rather than focusing solely on one disease. These look at patient and provider education, care delivery, and care transitions. Next slide.

I'll just leave you with some more information about how you might get involved with PCORI, or keep up with our work. Next slide. There are many ways to get involved. You can apply to serve on our advisory panels, become a merit reviewer, to review our research applications that are submitted, become an ambassador to spread the word about PCORI, or become a peer reviewer, who looks at our research findings at the end of our studies.

We need scientists, health care stakeholders, as well as patients to get involved in all these important activities we do. Next slide. Here's a list of our advisory panels. As I said, we have one focused on rare diseases that you'll see listed at the bottom. Next slide.

I encourage you to check out our website for more information on anything I mentioned today, and sign up to get our weekly newsletters to keep current on what we have going on. Next slide. Here's some general links to find out more information about the funding opportunities I mentioned, and you could always submit a request to our help desk if you would like more information. We have a lot of additional resources on our website related to conducting research, as well as engagement, that I encourage you to check out. Next slide.

Thanks again for the opportunity, and I'm happy to answer questions during the discussion portion.

CHAIR CALONGE: Thanks so much, Nora. I appreciate the information. And we're going to move on to Robyn.

DR. SAGATOV: Good morning everyone. Can you hear me okay?

CHAIR CALONGE: Yes.

DR. SAGATOV: Okay. Great. Hi. My name is Robyn Sagatov. I'm the Senior Advisor for Children's Health in the Office of Extramural Research, Education and Priority Populations at the Agency for Healthcare Research and Quality or AHRQ. I'm going to share some information with you about AHRQ and our funding opportunities. Next slide please.

Thank you. So, to provide some background about AHRQ, we are the lead federal agency charged with improving safety and quality of health care for all Americans, and to do this AHRQ develops the knowledge, tools, and data needed to improve health care system the health care system, and help consumers, health care

professionals, and policy makers to make informed decisions.

And our mission is to produce evidence to make health care safer, higher quality, more accessible, equitable, and affordable, and to work with the Department of Health and Human Services, and other partners to ensure that the evidence is understood and used. Next slide please.

So there's a link at the bottom of this slide to a site that has more details about AHRQ's research priorities. At a very high level, AHRQ's research priorities are to are research to improve health care quality and patient safety, improve health care delivery and practice improvement, and enhance whole person health care delivery. Next slide.

So, at AHRQ we have training and career development grants, like the R36, K01, and K08 awards. We have health services research grants, including R03 small research grants, R01's for large research grants,

U18 cooperative agreements, and large demonstration dissemination and implementation R18 grants, and then we also have R13's, which are conference grants. Next slide.

If you scan this QR Code, this will take you to AHRQ's website where you can learn more about our grant funding mechanisms, due dates, open notices of funding opportunity, and you can also sign up to be notified about new funding opportunities on that page. Next slide.

And this QR Code will take you to a page on AHRQ's website with all of the current notices of funding opportunities. Rather than reviewing each of them with you, I prepared a couple of slides with examples of awarded research grants or topics that would be of interest to this group, such as studies related to newborn screening, child screening, and children with rare diseases and/or medical complexity. Next slide.

So, the first example is an R01 submitted by

Dr. Lisa Prosser at University of Michigan, and Michigan Ann Arbor. This aimed to provide the necessary information needed for policy decisions regarding selection of conditions for newborn screening panels, and the study looked at health and economic outcomes for newborn screening using computer modeling, systematic reviews, expert opinions, surveys and stakeholder engagement, and focused on the evidence gap identified by this group. Next slide.

Next is an example R01 by Dr. Anna Kerr at Ohio University Athens, and this study related to primary care needs for patients with vascular anomalies, and aimed to improve continuity of care, and care coordination for rare diseases. And they were really looking at amongst the specialists for vascular anomalies, caregivers, and pediatricians, what the facilitators and barriers to care coordination for patients with vascular anomalies were. Next slide.

As an example, K award, this K01 by Dr.

Kendra Liljenquist at Seattle Children's Hospital had a goal to improve developmental assessment in primary care settings through specification of a computer adaptive developmental assessment that could be used by parents, clinicians and community health workers. Next slide.

Next is a K08. This was a grant by Dr. Arti Desai that aimed to improve the quality-of-care coordination for children's medical complexity, and this included participatory iterative design approach to a web-based care plan designed to meet family's needs. Next slide.

So, this slide includes some links to additional examples of awarded grants that you can review to get a sense of the types of grants that AHRQ has funded previously. I don't have time to go into them in detail, but feel free to take a screenshot, and you know, look into these in more detail, and I'm happy to chat offline about any of them. Next slide.

Another way that AHRQ does research is

through our evidence-based practice center, and we complete various types of literature used with this center, and we do accept suggestions for topics for evidence reviews, so there's a link on this slide where you could learn more about that. Next slide please.

This is just an example of a comparative effectiveness of treatment for PKU that was done through our evidence-based practice center. I know I'm running low on time, so I'm not going to go into more detail about that. Next slide please.

And finally, these are our notices of funding opportunity that are specific to patient centered outcome research. These are 2K awards, and they're research mentored career development awards. Next slide please.

So, thank you again for the opportunity to present about AHRQ's funding opportunities. My contact information is included on this slide, and I'm happy to answer questions during the discussion, or you're

welcome to contact me if you have questions, or research ideas. Thanks so much.

CHAIR CALONGE: Thanks Robyn. Now, we're going to turn to Melissa.

DR. PARISI: Good morning. Thank you for giving me the opportunity to speak with you all today. So, as you probably know there are 27 institutes and centers at NIH, and so I don't have the opportunity to tell you about all of the research being done, but I wanted to focus on some newborn screening programs, and particularly those that actually address some of the lived experience of patients and families. Next slide please.

And, I'm sure this audience is quite familiar with the Newborn Screening Saves Lives Act, which established the Hunter Kelly Newborn Screening Research Program at NICHD. This is named after Hunter Kelly, who was the son of Hall of Fame football quarterback Jim Kelly of the Buffalo Bills, and he died of Krabbe

disease.

So, this important legislation also specified the roles of various federal partners in the newborn screening landscape. NIH's role is to fund research, and we have four main components to our Hunter Kelly Newborn Screening Research Program to develop new screening technologies, to develop novel treatments, to provide research findings that will help support conditions under review to be added to the RUSP, and to conduct pilot studies to ensure conditions are ready for nationwide implementation.

And we use both dedicated grants and contracts to help support our research efforts across NICHD. Next slide please. So, innovative screening approaches are one of the types of funding opportunities that we support at NICHD, and we have two main categories, the integrative screening approaches and therapies for screenable disorders.

This basically is for potentially fatal or

disabling conditions that have been identified through newborn screening, or high priority conditions that have the potential to be identified through newborn screening. And you'll notice that these three funding opportunities have recently expired, but the R01, which is five-year awards and the R21, which is two-year awards, are in the process of being reissued.

And I would point out that one of the potential research objectives for a project responding to one of these PAR's is to include embedded studies that explore the ELSI related issues of novel screening technologies or therapeutic approaches. So, we try to build in patient feedback into many of our initiatives, and many of those who respond to these funding opportunities do include that element.

And then secondly, we also have another funding opportunity, natural history of disorders screenable in the newborn period, which was just reissued about a week ago, and this encourages

applications that propose to develop studies that will lead to a broader history of the natural history of conditions that are already on the newborn screening panel, or have the potential to be added.

Next slide. So, we also support contracts for I think we're a little bit further ahead than we need to be. Can you go back? Okay. Thank you. We support contracts that are large scale statewide pilot efforts for conditions that are recently nominated for the RUSP, or have recently been added to the RUSP, and basically we have a pool currently of three states that have the capacity to screen at least 100,000 newborns within a two year period.

And basically demonstrate the proof of concept for these new conditions, and potentially new technologies. We anticipate that the contractor pool will be recompeted in 2027. Next slide. And this is basically illustrates over the past ten years the different conditions and pilot studies that have been

supported under this contract mechanism, and the state or states that have successfully conducted those pilot studies.

Currently, the Congenital Cytomegalovirus study is being pursued at New York by HRI, and they also have a follow-up arm to determine the outcomes for those babies that screen positive and it's ongoing. And just recently as of two months ago in late September, we awarded an award to New York also to study Metachromatic Leukodystrophy in a piloted manner. Next slide.

So, those are sort of an overview of what we do at NICHD. I want to pivot and tell you a little bit about our colleagues at NCATS. NCATS is the National Center for Advancing Translational Sciences, and they support the Rare Diseases Clinical Research Network, also known as the RDCRN. This was established in 2002 under legislation, and currently supports 20 different consortia across ten different NIH institutes and centers of which NICHD is one.

These are currently in the process of being recompeted, in fact the reviews will be commencing very, very soon for the submitted proposals, and NICHD, in its list of preferred activities and high priority areas under this RFA, basically emphasized and highlighted newborn screening, newborn screening conditions as one of our areas of interest.

Each of the consortia, very importantly, needs to study three or more rare diseases, have multiple sites, conduct two to four clinical studies, including a natural history and longitudinal study, and have a pilot study program, as well as a career enhancement program to train the next generation of investigators.

But very importantly, have a fully integrated patient advocacy group as part of the consortium, and these are not just lip service. The PAGs, as they are known, patient advocacy groups, are integral parts of these awards, and they are absolutely essential for the

success of these projects. Next slide.

This is a list of all of the different consortiums that have been funded, and I don't expect you to read all of these, but I highlighted in yellow those that are either related to newborn screening conditions, or are conditions that have the potential to be screened in the future.

And you'll notice that on the right side there's a list of all those that have been funded under the past four cycles of the RDCRN. In 2018 it was decided that these were going to be sunsetted after having received at least three cycles of funding, so the top 11 consortia are no longer going to be able to compete in this next round, and we anticipate that we will be awarding a large number of new rare disease consortia, and we hope that some of them will also involve rare diseases that are related to newborn screening. Next slide.

And then finally, the success of this program

is multi-fold, but it has really had a significant translational impact. Many clinical trials, early faced clinical trials have been supported directly by these cooperative agreements, and there have been many associated clinical trials that have been supported by industry partners or foundations, or other groups, much akin to what Dr. Hu was describing earlier on today.

And the results of these trials is that there have been 12 FDA approved treatments for 11 rare diseases over the past several years. Next slide. So, now I'm going to pivot and tell you a little bit about our colleagues at NHGRI, and some of their programs.

I know we've talked about ELSI before, and I've mentioned the acronym before, and I think most of our are aware that ELSI stands for Ethical Legal and Social Implications, specifically in relationship to genetic and genomic research, and that's really what NHGRI, the National Human Genome Research Institute has embraced with regard to its emphasis on promoting

understanding of really, what are the real world implications of funding research in genetics and genomics.

So ELSI research is multi-disciplinary. They fund a number of different, again PAR's, program announcements, related to different bread and butter mechanisms that are utilized across NIH, and then they also have a relatively new program to advanced ELSI research that includes partnerships with relevant communities affected by, and with an interest in the proposed research.

So, these are again, cooperative agreements that involve considerable input from the family and patient community. And so, this new program is called the BBAER Program, Building Partnerships and Broadening Perspectives to Advance ELSI Research. And I can tell you that over the years NHGRI has supported a fair amount of research related to newborn screening conditions. Next slide.

And one of the other major endeavors that NHGRI has pursued is something known as the clinical genome resource or ClinGen. This is an NIH funded project that's dedicated to building an authoritative, central resource that defines the clinical relevance of genes and variants for use in precision medicine and research.

The goal is to really understand which genes and variants are associated with disease, and how genomic information can inform clinical care. If you look at the upper left of this particular slide, you'll see a little circle for patients, and essentially that leads us to the discussion of how these different components, patients, clinicians, laboratories or researchers, can all input data that can inform the determination of whether or not a variant in gene is pathogenic.

So, next slide. A component of ClinGen is actually Genome Connect, which is the ClinGen patient

registry, and this is really developed because ClinGen felt strongly that patients could serve as a very important source of additional information to inform the curation of genes and variants.

So, in 2014, they launched this patient registry called Genome Connect, and essentially it's open to anyone who has a genetic testing result, whether or not they have a diagnosis. They can input their data. So, essentially participants enroll online, consent to de-identify data sharing and recontact, provide their health history through patient surveys, and upload a copy of their genetic test results.

In addition, they can potentially receive genetic testing updates with regard to the pathogenicity of their variant or variants, and they can also connect with other families and patients who may have similar gene variants that cause disease through matchmaker exchange.

So, this is another very powerful tool that

really engages patients in helping with the research endeavor. Final slide, next slide. Well, essentially it's my thank you slide, so that closes for me, and I want to thank you for your attention, happy to take questions.

CHAIR CALONGE: Thanks, Melissa, and finally Catharine?

DR. RILEY: Hi. Good morning, and thank you to the Committee for the invitation to participate on this panel. It is very nice to be back with the Committee today. We were asked to share with you the type of work we support in this space of lived experience of individuals living with inherited and rare conditions.

Today I will focus primarily on the qualitative research we support, but first I wanted to share a couple of other ways we include the experiences of individuals, families and communities in our work. Next slide please. So, first I want to touch on how we

gather and share stories of individuals living with the conditions that we study, as well as stories from their families and caregivers. Next slide please.

It's important for us to learn from the stories and experiences of the individuals living with the conditions we study in the National Center of Birth Defects and Developmental Disabilities. We do this in a number of ways. We have written stories from the individual and family perspective on our website.

You can see a few of those stories depicted here on the slide for sickle cell disease and thalassemia. We work with individuals and families and the community to make videos to share on our website and across social media platforms. You see a couple of examples of those here on this slide as well.

And our colleagues in the molecular branch at MCH also have a webpage where they share stories related to individuals with conditions identified through newborn screening also depicted here on the slide.

So, it is important to share these stories broadly, but it's also important that as we gather these stories we are learning from these shared experiences, and incorporating that knowledge as we plan and share our work moving forward, and shape our work moving forward. Next slide please.

So, next I just wanted to highlight how we engage with community partners to both inform our work, and help us collectively disseminate information and findings. Next slide please. The sickle cell data collection program is a public health surveillance system that collects health information about people with sickle cell disease to study long-term trends and diagnosis treatments and health care access for people with sickle cell disease in the U.S.

Each SCDC site has a multi-disciplinary advisory team that includes health care providers, researchers, community-based organizations, people living with sickle cell disease and their caregivers,

public health practitioners, and policy decision makers. The SCDC program developed a community outreach work group to bridge the data to translation gap between the community-based organizations and scientists to improve the lives of people with sickle cell disease.

What they learned in this process is highlighted here on the slide, and this ranged from the importance of prioritizing trust building to foster an open communication to incorporate in community voices from the very beginning. Next slide please.

In 2009 various organizations across the federal, state and local communities came together and agreed that they could positively impact the health of those affected by congenital heart defects by utilizing a public health approach to address many of these issues that the community faces.

So, we supported the American Academy of Pediatrics to develop the formation of the Congenital Heart Public Health Consortium, comprised of

organizational members representing voices of providers, patients, families, clinicians and researchers. And you can see more about the organization on this slide, and also online, and this organization is still growing strong today. Next slide please.

We also incorporate the experiences of individuals living with the conditions we study by building that engagement into the work through inclusion on advisory boards and strategic planning efforts. So on this slide here it's two examples of projects the National Center of Birth Defects and Developmental Disabilities currently is funding that have built in community inclusion across the funded activities.

Next slide please. And although we do not have any current open notice of funding opportunities that focus on the lived experience, we do have many ongoing efforts that include this type of work, so I want to share a few examples of qualitative studies our center either previously funded, or is currently funding

that help us understand more about the lived experience of the populations we study, and can contribute to the overarching knowledge base. Next slide please.

This year we worked on efforts to reach Hispanic Latino women, age 24 to 35. The theme this year for Hispanic Heritage Month was a mother's love, roots of life with folic acid. These efforts were informed by formative research with a target audience where we learned about knowledge, attitudes and practices around folic acid, and fortified food consumption.

Preliminary findings helped guide the outreach to educate Hispanic and Latino women, and their support networks about the importance of taking folic acid to help prevent neural tube defects. One outcome was the development of these videos, Tips from Abuela's Kitchen, as depicted here on the slide. These were short videos in English and Spanish that focused on incorporating folic acid into traditional dishes, while

incorporating culturally relevant elements. Next slide please.

We also collaborated with the American Academy of Pediatrics to conduct focus groups to understand more about the challenges and barriers experienced by Latino population living with spina bifida. The focus groups were conducted with a total of 28 participants earlier this year by Zoom, in English or Spanish, based on preferences.

A big thank you to the AAP Birth Defects and Infants Disorders Teams for sharing this information. Next slide please. The goal of the study was to better understand the health care experiences of Latinos with spina bifida and their family members in accessing care, identifying existing gaps in care, and gain a better understanding of any cultural and linguistic barriers that may exist. Next slide please.

Five themes emerged, which are listed here in the slide. In the interest of time I'll just share some

excerpts from two of the focus areas. Next slide please. Participants expressed frustration with barriers they encountered in accessing central health care services, so for individuals with spina bifida, the main issues were insurance coverage limitations, the financial burden of medical expenses, as well as challenges accessing doctors and specialists.

And similarly, parents and caregivers shared about their challenge in securing specialized treatments and support for their children. They discussed the emotional and financial toll of managing their child's medical needs. Next slide please.

Transitioning from pediatric to adult care presents a significant challenge for individuals with spina bifida, and I think this goes for many conditions, so many complex medical conditions that we all work on. Participants highlighted issues such as discontinuity of care, the difficulty in finding adult care specialists, and adapting to new health care providers, and the lack

of mental health support for navigating these transitions effectively.

Next slide please. Here are just a couple of examples of focus groups or discussion groups that we're currently supporting through cooperative agreements with the American Academy and Pediatrics, and Oak Ridge Associated Universities. AAP is connecting focus groups with parents and caregivers of children with birth defects and infant disorders to inform the development of strategies, resources, and technical systems for clinicians and families.

And ORAU is implementing discussion groups of peer support workers, and pregnant and post-partum participants to learn more about knowledge, attitudes, beliefs, behaviors and training needs. Next slide please.

We're also currently connecting focus groups, about 40, up to 40 focus groups across multiple conditions, including congenital heart defects, muscular

dystrophies, and spina bifida. We hope that these focus groups will help us fill critical knowledge gaps, shape interventions, allocate resources, and inform clinical care. Next slide please.

So you can see here for congenital heart defect focus groups will be focusing on adults that have been out of care for more than three years. And for muscular dystrophy focus groups we'll be focusing on both adults living with several types of muscular dystrophy, as well as care givers of children with early onset types of muscular dystrophy.

And we hope that we can explore sources of clinical care barriers to accessing care, the journey to diagnosis, and transition from pediatric to adult care. Next slide. And this is my last slide, and this is just to highlight the focus groups that we're doing as part of that larger effort for spina bifida, and again, these are funded under a contract with KRC Research. And the spina bifida focus groups will be doing up to nine of

those, are going to be with adults living with spina bifida, and also caregivers of children, and then focus groups caregivers of adults with spina bifida.

And next slide. So, the work I shared with you today expands beyond the conditions that the Committee may be focused on, however, I think we can learn across these complex medical conditions, and apply what we learned from all the experiences across populations that we serve, and learn how to better incorporate the lived experiences into all aspects of our work. Thank you.

Committee Discussion

CHAIR CALONGE: Thank you so much. And thanks to all our speakers, we'll move into the question and answer session, discussion session. Sorry, I will prioritize Committee Members first, and then our Org Reps second. I appreciate input from all. I do want to point out that the slides went by quickly because we

gave our wonderful speakers short periods of time, and they will all be available on our website soon, after the meeting, so I appreciate that.

And I might start with a question for Nora if I might. I'm intrigued by thinking about CER for rare diseases where comparative effectiveness studies require having lots of subjects, and newborn screening detects very rare conditions. And so, I was trying to get an idea of how that interplays, especially with rare disease advisory committee, and would something like a study that looked at the usual care, or usual time of diagnosis compared with birth detected diagnosis fit under the rubric of a comparative effectiveness?

DR. MCGHEE: Sure. Happy to tackle that. So, we have a lot of studies in our portfolio with usual care as one of the comparators. We are open to that as a reasonable comparative. We do have a methodology standard around the requirements for usual care related to that it has to be, you know, adequately described and

measured throughout the course of the study, so that it's not kind of an amorphous comparator, so it can be reasonable comparative to the study.

As far as, you know, the feasibility in general of doing rare disease CER, it can be a challenge, and our advisory panel has been informing our work, and as I said we had a recent funding announcement that we hope to put out some announcements soon for that.

I think we are encouraging cross cutting work where there are research questions that cross multiple rare diseases to help get around the small numbers problem, and I think we do have a number of studies, as I said, over 40 studies that focus on rare diseases, and most of them are pretty focused on specific rare diseases.

So, it's really a question of kind of what the right research question is, and if you expect a large enough difference between the comparators that you

can get away with a relatively small number in your sample size.

CHAIR CALONGE: Just a quick follow-up. I really appreciate that answer, it's very helpful. One of the things I've always appreciated about PCORI is that it's patient centered. So, you look at patient centered health outcomes, and we're thinking about how to actually also capture family centric health outcomes, so when the actual involved patient is one consideration, but the impact of the family on comparative methods of detection or comparative therapies might also be really important.

Does that fit within the conceptual framework for PCORI work?

DR. MCGHEE: Oh yeah, of course. I mean just because we're named the Patient Centered Outcomes Research Institute, it doesn't mean we're narrowly focused on the patient only. It's really the patient, and it lives within the family, and within the larger,

you know, care ecosystem of their caregivers, and also their clinical team. So, it's really as I said, we really emphasize engagement of the right players in developing the research question, and the research plan, and that should involve patients, caregivers, and kind of all the relevant stakeholders.

And they should be shaping which outcomes are chosen for the research study, and those could include patient reported outcomes, patient clinical outcomes, but also family outcomes. It's really what's most important to answer that research question and that will provide the most useful research findings at the end of the study.

CHAIR CALONGE: Thanks, Nora, that's a great answer. I really appreciate it. Let's see. First up I have Bob?

DR. OSTRANDER: Thank you. I'm surprised I don't have any Members ahead of me. I have a little concern listening to all that you have said. This isn't

focused to any one person. I think it's hugely important that we have, you know, patient advisory boards on these various projects and research panels for all sorts of reasons, but I don't know that having an advisory board constitutes lived experience research.

I'm concerned about selection bias problem, and I'm sure that's really been the challenge in my mind, about this lived experience research. People who come forward with their stories are leaders in their advocacy groups, may not really represent the population that we want to research the lived experience on. And I imagine it's incredibly difficult to get a good sample of lived experience research.

I mean some of the focus group work that we've heard about in the last talk with Catharine, you know, sort of reaches that. I was involved in a project with SCID at one point. But I'd be interested to hear, you know, aside from including the patient's advisory groups, and something designed for, you know, more

standard research, how we deal with the selection bias in doing real lived experience research.

CHAIR CALONGE: I assume you're throwing that open for any of our experts who would like to answer.

DR. OSTRANDER: Yeah. Again, it wasn't any one thing. I mean all the talks there was a lot of talks about including patients on advisory boards, to make sure that the right questions got asked during the research. But then actually doing the research of the lived experiences, and getting a broad representative sample of patients either with a condition, or you know, our struggle all the time with this panel has been of the patients who are screened, they get the false positives, plus the ones that are screened, et cetera, et cetera.

But even if you go to the treatment limb, you know, how do we get a representative sample for lived experience as opposed to just those who volunteer to be on the advisory boards, our leadership in the advocacy

panels, and all that. Again, it's not to negate the value. It's critical that you have patient advisory boards in the study design, so you ask the questions about things that are important to patients.

But it's not the same as doing real research about lived experiences where you need to look at a sample size, and you want a wide selection of that.

CHAIR CALONGE: Thanks, Bob. Melissa?

DR. PARISI: Bob, I don't know if I can answer your question about completely avoiding selection bias because I think that's very, very challenging, unless you sample the entire constellation of folks with lived experience. I mean obviously there's a lot of variability.

I will say that one of the strategies that I think has been more effective is engaging families and individuals earlier on in the process, so prior to developing the study design. There was a very illustrative example that I learned quite a bit from

with one of the rare disease consortia, that proposed to do a change to the dietary intervention for a given rare disease, and the problem was that they had not actually gotten buy in from families.

Families, even if that treatment was not really demonstrated to make a huge difference in the outcomes of their kids with this rare, devastating neurologic condition, felt like it was the one thing they could do. So, asking them to go off this particular dietary intervention, even for a couple weeks, and switch to something else was just a non-starter.

So, if they had actually engaged those families, and those patient advocacy groups before even designing the study, I think the chances that they would have stumbled into a failed project, to be honest with you that just never actually hit its recruitment goals, would have been alleviated somewhat.

So, I think involving individuals as co

researchers, that means they're part of your team, and you may even need to compensate them for their participation, is actually one of the strategies that can be used. You still may not address all of those issues of bias, but it's one approach that may be somewhat successful.

CHAIR CALONGE: Thanks, Melissa. Catharine?

DR. RILEY: Yeah, thank you, Bob. I think and what I was trying to highlight in the presentation was that there are multiple ways we can be inclusive along the way. So similar to what Melissa had indicated. And I think for the resource component doing the qualitative research. So whether that be focus group or key interviews, or maybe a phenomenological study about the lived experience for a particular condition.

I think those are also really important, so it's not that they're all the same, it's just different ways we can incorporate the community, the individuals

and their experiences, in the whole process. But certainly I think, the research component, and then being able to publish those results so they become part of the broader knowledge base that we can then collectively draw on is important.

And so, for many of the focus group, and key from interview projects that I mentioned, the goal is to then publish the results of those that that becomes part of the knowledge base.

CHAIR CALONGE: Thank you, Catharine. Mike?

DR. HU: Thanks, Rob, for the questions. In addition to what Melissa and Catharine has mentioned, I just wanted to give a quick shout out to HRSA's current efforts. Maybe Jeff can detail that a little bit, but I'm going to work to systemically improve how we do lived experience as research, and at the research networks that HRSA is funding.

I think those are ways to address, hopefully, part of the potential bias questions, and make our lived

experiences research more complete in the future.

CHAIR CALONGE: Thanks. Michele?

DR. CAGGANA: Michele Caggana, Committee Member. I agree with Bob and Melissa. I was thinking about that as Bob was talking about sort of the ascertainment bias, and that's something I always worry about in these kinds of studies. And along those lines I think it's really important as Melissa said, to be sure that the research is actually truly patient driven, and not hey, let's get some patients together, and come up with a project, and then use the patients to prove our point.

The other thing I was wondering with some of these other patient driven research, several organizations out there that sponsor that we heard about today, is there any way that some of these opportunities could be sort of placed in one area, because someone has to really know to go look at this organization, and that organization, in order to find these opportunities.

And I was wondering if there's a home where they could live sort of together? I guess not.

CHAIR CALONGE: I think, Michele, you might be providing food for thought that our speakers and the different organizations they might be prompted to think about how these efforts could go together. Jeff?

DR. BROSCO: Actually I'm going to respond to something that Mike raised before, so I'll let maybe Nora has a specific answer to her question.

CHAIR CALONGE: Nora?

DR. MCGHEE: Oh, I was just going to say briefly that we could certainly talk to our communications folks at PCORI about publicizing this in ways that publishing PCORI's research opportunities, and engagement award opportunities in ways that might be more accessible, and a place for folks to find them. We always are hoping for that.

DR. BROSCO: And this is Jeff. And I think I just want to really make a clear distinction between a

couple things that have come up. I think both Michele and Rob got involved brought up. And that is that what we're talking about is including patients and families, and people with lived experience throughout all aspects of all research, right?

So, not just research that's about patient outcomes. So, for example, in the Krabbe research that we looked at, remember that we heard from families. Irritability is one of the most important things for how we experience our child, and it's really awful, and we really need to address this. We heard that from a number of folks, including clinicians as well.

And if you look at the research though it wasn't say the irritability scale, asking parents did things get better once you had a bone marrow transplant. So, something that was really important to families was not included in the outcomes of the research.

And so this is the ascertainment bias is true of all research we do all the time. And the idea of

making sure that families and patients with lived experience is included from the beginning means that the outcomes that you look at, right PCORI, patient centered outcomes, the outcomes that you look at are the ones really relevant to families and patients.

So, the ascertainment questions are for sure there, especially if you have a patient, you know, involved in trying to help you figure stuff out, but the idea is that we should be all of our research should be focused on these kinds of things. And if you think about what we've done as a Committee over the last year and a half, we've said well, how do we make sure that the public comments, the voices of families, and people with lived experience, gets included in the evidence base?

And we had a series of speakers that talked about the ways he did it, and today it was great to have you, Mike, and our federal partners, talk about all the different ways that this is already being done, and some

of the funding mechanisms available.

And the last thing I want to add is that this is, and Mike you brought this up, and you talked about this before, this is absolutely not trying to add yet another hurdle, another thing for nominators to have to do. This is to make sure that the research we're already doing includes a way of making sure that the outcomes include what matters to families.

And at HRSA we find relatively small amounts of research, and what we're really focused on in our research network that you brought up a couple times, is making sure we have good measures of family outcomes. And I think we're planning a presentation a little bit later to talk about how we're doing this in newborn screening. Thanks.

CHAIR CALONGE: Thanks, Jeff. Natasha, last question before lunch. Not to put on pressure.

MS. BONHOMME: No pressure, it's okay. Natasha Bonhomme, Genetic Alliance. Thank you for the

presentations. I have a comment, and then a question. You know, I think this discussion around ascertainment bias is a really important one, but I do notice that it tends to come up quite frequently when we're talking about patients, and patient perspectives and lived experience, and doesn't necessarily always come up in other parts of research where we know that can also be the case, right?

Depending on which clinicians you may be speaking to around a certain topic, there may be some bias there, so just trying to think of, you know, this important topic, and putting it in a broader context of, you know, people have biases in different ways because of different reasons, and just thinking about that.

And it was noted, you know, thinking about, you know, there's some advocacy groups that are really strong leaders, and have a very strong voice, and have a range of different mechanisms to engage their memberships, and I think that's similar to professional

societies. There are some professional societies that are super tapped in with their membership, and all their members seem to be really excited, and others, not quite the same.

So, just putting it within that context. My question to all of the panelists is really about compensation and broader support for families to be able to participate. You know, we still see at Expecting Health, families being invited to advisory committees, being asked a lot of questions, and not being necessarily provided any compensation or very miniscule compensation, like a gift certificate.

Whereas, you would never ask a Ph.D., a PI or Co PI to do that work based off of, you know, gift certificates, or smaller stipends, you know. We know that this is their living. So, just wanted to see from your perspectives, you know how your agencies or organizations have dealt with that, or are thinking about that type of compensation, so that you can get

families who have a range of experience involved in many different ways. Thank you.

CHAIR CALONGE: Nora?

DR. MCGHEE: Yes. So PCORI has a compensation framework for stakeholder partners, including patients and caregivers, as well as our foundational expectations that guide how they should be involved throughout the process, and properly compensated, so I really encourage you to check out our resources because we really think it is a really important topic, and agree with the points you're making wholeheartedly.

CHAIR CALONGE: Mike?

DR. HU: That's a great question. I just want to share a little bit of our own experience. We do provide a small token of appreciation to the families who enroll in the GUARDIAN study, as we do a lot of surveys, the exit survey, the non-participant survey, and the follow-up survey, so we do show that.

I think it is in general appreciated by the participating families, in particular I think for the families who are affected, and as most of the applicants in the areas will be. Families are certainly very motivated to share. So it's not so much of a question that we necessarily need to compensate them, but I think it is recognizing that this will help more families participate in the research because some of them are probably not in best positions to, you know, take up an hour or two out of work to participate.

And so, I think this is more of a way to enable those advocates who might not otherwise have the opportunity to participate, and it helps to address the ascertainment bias that was mentioned earlier as well.

CHAIR CALONGE: Thanks, Mike. Melissa?

DR. PARISI: We encourage our investigators to compensate families whenever it's feasible, and in fact, for some of our down syndrome related activities, we actually use a gift fund to compensate self-

advocates, and advocates who participate in any of our webinars, and receive an honorarium, and that is not a trivial sum of money.

And we also host workshops. And when we invite self-advocates with down syndrome to speak, and/or help out as greeters, or whatever they are doing, we also provide compensation to them. And I think what it really shows is that you respect their presence. You welcome their commitment and their input, and you really want to make sure that they are, you know, being appropriately rewarded for their participation. Thank you.

CHAIR CALONGE: Well, this has been a great panel. I really appreciate everyone's input. The presentations were thoughtful, full of information. I think what we were really after was what you presented.

How we can do things, how we can start to think about opportunities to fund and conduct research, that includes the very important outcomes of impact on

families and patients outside of what we often numerically count for the lived experience of both.

It's just so important, so I really appreciate your time today, information you shared, and I hope that our community looks at the rich opportunities available to us in designing research that can inform our evidence review group, and our decision making going forward.

Lunch

CHAIR CALONGE: We're going to move into lunch, and we're running a little late, so in a show of generosity, I'm going to extend lunch until about 12:35 Eastern Time, so five more minutes. Let's try to restart at about 12:35 Eastern, and we'll see you all then. Thanks.

(Lunch Break 12:00 p.m. 12:39 p.m.)

Public Comments

CHAIR CALONGE: I think we're just missing one person, so I'm going to go ahead and respect the time, and the resource that we have in our folks presenting public comments, and I have an order, and I'm going to follow that. And W.G. Stuart Mackenzie, you are first. I see you.

DR. MACKENZIE: Good afternoon. Thank you very much for this opportunity to speak before the Advisory Council today. My name is Stuart Mackenzie, and I'm a pediatric orthopedic surgeon here at Nemours Children's Hospital in Wilmington, Delaware.

It's my great pleasure to speak to you in advocacy for patients and families with Mucopolysaccharidosis, Type 4 A, otherwise known as Morquio Syndrome. I serve as the Surgical Director of our multi-disciplinary dysplasia program here, and I'm proud to say that we are the country's foremost program for patients with rare skeletal dysplasias.

I'm very involved in researching and treatment of children and young adults with Morquio Syndrome, including an NIH funded study under which I see nearly 100 patients per year. To date, I would describe our treatment of patients with Morquio Syndrome as entirely reactionary.

Classically, these patients are diagnosed after the age of three years old, as they are born appearing typically developed with physical manifestations of their lysosomal storage disorder which begin at birth, yet take years to become apparent. This diagnosis can be delayed even further in many cases, and multiple times I've met families, and had to discuss urgent the need for urgent surgical decompression and spine fusion at that first visit.

The surgical burden on these Morquio patients is incredibly high, and I'm very proud to provide improvement and quality of life for my patients, but I'd be much happier keeping these patients healthier and

more active with less surgery. I've looked forward to a time when we can be more proactive in the care of these children.

Currently, our medical community has an excellent treatment option for Morquio Syndrome in the form of enzyme replacement therapy. Weekly infusions provide the deficient enzymes to our patients, and results in benefits of muscular endurance, decreased fatigue, and improved pulmonary function. We know that early initiation improves function.

With our current dysfunctional diagnosis pathway, many patients are receiving the enzyme at an advanced age. This treatment has been proved to be safe and effective. It is approved and in use around the world, but our patients deserve access sooner. My partners and I here at Nemours are currently involved in researching a gene therapy option for these patients, and I look forward to the day when our patients can have both early diagnosis and early access to care.

And so, for this reason today I'd like to strongly support the need for newborn testing for Morquio Syndrome, to give these bright and capable children every opportunity available to them.

CHAIR CALONGE: Thank you so much, Stuart.

DR. MACKENZIE: Thank you.

CHAIR CALONGE: For your great comments. I'd like to now turn to Christine Tippett. I don't know that I see Christine.

COMMANDER MANNING: She hasn't joined yet.

CHAIR CALONGE: Okay. We will return and see if she does join us coming up. And so, I'd like to turn to Abbey Cook. I think you need to turn on your microphone.

MS. COOK: Good afternoon, and thank you for this opportunity. Are you hearing me now?

CHAIR CALONGE: Yes.

MS. COOK: Okay. Good afternoon, and thank you for the opportunity to share our story. My name is

Abbey Cook, and I'm here on behalf of my sons and the CTX Alliance, the sole patient advocacy group dedicated to Cerebrotendinous Xanthomatosis, or CTX. We look forward to submitting a preliminary nomination early next year for your consideration to add CTX to the Recommended Uniform Screening Panel.

Today, I wanted to share with you the Cook family's experience with CTX, so that your Committee and others understand why newborn screening would be life changing for families like ours. In their first ten years, our beautiful and clever sons, Ben and Zach, were diagnosed with a series of cognitive and physical issues.

Learning disabilities, central auditory processing, speech, and executive function disorders, hand tremors, nystagmus, GI problems, and for Zach, behavioral issues. We sought out the best therapists and doctors, arranged school accommodations, and supported their needs as best we could. The next decade

brought even more diagnoses, ADHD, non-verbal learning disorder, and for Zach, Autism spectrum disorder.

Meanwhile, our daughter Becky, untouched by these issues, helped her younger brothers, but she was profoundly affected by their struggles and our growing distress. In his 20's Zach's health took a steep decline. He became troubled, withdrawn, and sometimes talked about ending his life.

He slept excessively, had psychotic episodes, and no doctor, not even a leading neuropsychiatrist at an elite medical school here in Boston, could diagnose or slow Zach's deterioration. Ben, his older brother and best friend felt he could no longer recognize Zach.

All of us grieved as a feeling of helplessness took hold. Then, at age 26, Zach's achilles tendons began to swell. An MRI revealed Xanthomas, but it took four more years for us to learn of this finding, and to discover that these swellings and Zack's other symptoms pointed to CTX.

When I searched for images in medical journals of achilles tendon xanthomas, they looked just like Zach's. The xanthomas were caused by a rare disease called Cerebrotendinous Xanthomatosis, a disease also causing devastation in the brains of these patients.

My husband and I immediately requested confirmatory diagnostic testing. Zach was finally diagnosed two years ago, which led to Ben's diagnosis as well. Zach's 30 year ordeal has saved his brother's life. Today, our sons are fortunate to receive specialized care from the team at Mass General, and from laboratory researchers, like Dr. DeBarber.

The disease has left an indelible imprint on us, and continues to injure our sons' bodies and minds. Treatment at this stage of life, after the disease has been untreated for more than 30 years, can only do so much. We, especially Zach and Ben, face the consequences of a late discovery of this progressive,

but highly treatable condition.

Newborn screening for CTX would allow families like ours to intervene early when treatment could prevent or halt the progression of symptoms, and to avoid a diagnostic odyssey like ours. Thank you for considering the impact newborn screening would have on CTX families, and for listening to our experience with this disease.

CHAIR CALONGE: Abbey, thanks so much for sharing your story. We appreciate it. I'd like to now turn to Robert Steiner.

DR. STEINER: Hello. I'd like to thank the Committee for the opportunity to share some thoughts about newborn screening for Cerebrotendinous Xanthomatosis. You heard Abbey Cook's eloquent presentation, and unfortunately the story of the delayed diagnosis is all too typical in CTX.

My name is Robert Steiner, and I'm a physician scientist and newborn screening professional

at the University of Wisconsin School of Medicine and Public Health. I do not represent the University or the state today, but rather I'm speaking on behalf of the CTX Alliance, a patient advocacy organization that intends to submit a preliminary nomination for consideration of CTX for addition to the RUSP.

I'm an officer of the CTX A, and also disclose that I have served as a consultant for companies that market treatment for CTX. I've diagnosed and cared for patients in CTX for more than two decades, and I'm supporting efforts to implement newborn screening for CTX because I've witnessed firsthand the benefits of early diagnosis and treatment of the condition.

CTX is a genetic metabolic disorder caused by mutation of the CYP27A1 gene, which encodes an important enzyme in bile acid synthesis. Deficiency leads to impaired production of bile acids, in particular, chenodeoxycholic acid, or CDCA, and accumulation of

cholestanol and bile alcohols, which leads to the diverse clinical signs, and symptoms of CTX.

CTX presents with a wide spectrum of life altering clinical manifestations that can vary significantly in onset and severity. In infancy, affected individuals may experience liver disease that can resolve, but also can be fatal. Chronic diarrhea is usually present in infancy, and can significantly impact growth.

Additional childhood symptoms may include bilateral juvenile cataracts, seizures, and intellectual disability. As the disease progresses, spastic paraparesis, cognitive decline and dementia ensue. Psychiatric symptoms are also common from childhood onward, and may be completely debilitating.

Additional features as you heard, include Tendinous Xanthomatosis, heart disease and osteoporosis. Now, CTX is an infancy and childhood onset relentlessly progressive disorder. The condition

is not divided into mild versus severe, or early versus late sub-types. The range of birth prevalence for CTX is estimated at about one in 70,000, and one in 234,000 depending on the population study, and that represents the most recent estimate.

CDCA, in the form of a simple tablet, taken three times a day has been used for 40 plus years as the standard of care for treatment of CTX. Since initial trials showed it was safe and effective to stabilize, or improve symptoms and prevent disease progression. Additional clinical evidence includes data from long-term treatment studies that have further shown that initiating CDCA therapy at an early age correlates with better outcomes.

In some of these studies, younger siblings benefitted from their older sibling's diagnosis, and showed that treatment in childhood can prevent disease symptoms. A recently published consensus clinical guideline suggested that treatment start at diagnosis,

even in infancy.

CDCA is currently FDA approved for treatment of gallstones and is prescribed off label in CTX, although it is considered a medical necessity for patients with CTX, by both the FDA and the NIH. A study to demonstrate CDCA's safety and efficacy, has recently been completed with a result in new drug application for CDCA and CTX that is currently under consideration by FDA.

Colic acid, and alternative therapies, already marketed for bile acid synthesis disorders. An average two decade long diagnostic delay still persists, due to the rarity, as well as variability and presentation of CTX with symptoms overlapping with more common conditions. Based on prevalence estimates, CTX is significantly under diagnosed, and yet confirmatory diagnostic testing is widely available.

Universal newborn screening is the best approach to mitigate late and under diagnosis. Early

identification, diagnosis and treatment are critical to arrest disease progression, and prevent often irreversible, intellectual and physical disability. Newborn screening would also spare families the burden, both financially and emotionally, of the average two decade long diagnostic odyssey that you heard a bit about so eloquently from Abby.

Tandem mass spectrometry methods to screen newborn dried blood spots for CTX have been described and successfully further tested, using instrumentation and general procedures, already in use in newborn screening labs. We greatly appreciate the opportunity for efforts toward newborn screening for CTX to be discussed today.

It's a devastating disease that is typically diagnosed too late to prevent severe complications. Newborn screening can change that. We thank you for the continued hard work of the Committee on behalf of children affected by rare diseases for whom newborn

screening will provide tremendous benefit. Thank you.

CHAIR CALONGE: Thank you, Robert. Next we have Brandi Yoko.

MS. YOKO: Hi. I just want to make sure my stuff is working. Okay. I wanted to thank Dr. Calonge and the Committee for allowing me to speak today. My name is Brandi Yoko, and I'm here on behalf of BARE, Biliary Atresia Research and Education in support of adding Biliary Atresia to the RUSP.

I'm eager to see their application move successfully through this process as early diagnosis is imperative to possibly avoid transplant or death, associated with this disease. My son was born in February 2022, when the common understanding was that the surgery needed to diagnose and treat this disease, known as the Kasai, was most effective if done within the first six to eight weeks.

We now know, based on several reviews of studies worldwide, that it actually has the best chance

of working within the first 30 days of life. Currently, the majority of BA babies are diagnosed on average around three months old. My son got his Kasai at six weeks exactly, and it pretty much failed immediately.

He was evaluated for liver transplant less than a month later, and was listed in August. His paternal aunt was thankfully deemed a near perfect live donor match, and he had his transplant in November 2022. Many people seem to think transplant is kind of plug and play, but it's far from due to the side effects, the biggest being from Tacro, which most transplant patients will require for life.

A month post-transplant, my son got EBV. A month after that, an ulcer found in his duodenum resulted in a diagnosis of EBV positive, monomorphic PTLD, consistent with the diffuse large b cell lymphoma, due to the immunosuppression allowing the EBV to grow.

A severe case of Norovirus two days later resulted in needing Rituximab infusions for the PTLD.

He was taken off Tacro during that time to let his immune system kick in against the EBV, and has since had two episodes of mild rejection over a year apart, the most recent being this past June with his liver enzymes still being unstable.

Along with PTLD, he has been diagnosed with FPIES after ruling out ELE, and has a brain MRI scheduled next week for central sleep apnea found this past April during a sleep study ordered due to breathing issues from adenoid hypertrophy, before starting on Flonase.

Unfortunately, none of these are uncommon post-transplant complications. Throughout all of this, I still have to work. I take Teddy to his appointments, and any emergency trips or hospital admissions, but I have to ration my PTO, so I work extra around these events, as having a medically complex child isn't cheap in this country.

We still mask. Neither of my children have

gone to daycare or preschool yet, until Teddy's liver is stable, and most family events take place outdoors if we even join at all. My son's transplant hospital isn't one that gives the MMR or Varicella vaccines to transplant patients, so in today's ever growing anti vax climate, sending him to school is a terrifying thought.

Transplant is a marvel absolutely, and my son would not be here without it, but I know far too many babies who didn't make it because of a late diagnosis, or complications from transplant. Avoiding transplant is the most desirable outcome that every BA baby and their family deserves. And the change of one simple test from a total to a split bilirubin test, directly after birth, or by the first two weeks of birth, can diagnose this disease in time to have an effective Kasai performed.

Unfortunately, most of the physical symptoms can be excused away until it's too late, so this is the best way to help avoid a late diagnosis. About 50% of

the pediatric patients currently on the transplant list, are for livers. And Biliary Atresia is currently the number one cause for pediatric liver transplant.

This one simple test change from a split, or from a total bilirubin to a split bilirubin could keep other babies from experiencing everything that my son and others have had to endure. Thank you for letting me speak today.

CHAIR CALONGE: Thanks so much, Brandi, and thanks for sharing your story. And I know your schedule is busy. I'm glad that you had time to present today. I appreciate your presence and your comments, thanks so much.

Next I have Tebyan Rabbani.

DR. RABBANI: Good afternoon. Thank you for this opportunity. I'm Doctor Tebyan Rabbani from Stanford University's pediatric GI department. Today, I want to share a story about the profound need for newborn screening for Biliary Atresia, the number one

cause of solid organ transplants in pediatrics.

Early in my training I encountered a mother concerned about her baby's yellow eyes and skin. She told her pediatrician, "My baby's eyes are yellow." Her concerns were dismissed with explanations like, "Sometimes Black babies have yellow eyes." I still have no idea what that comment even means.

Jaundice lasting longer than two weeks of life is not something to be dismissed lightly. Her child had Biliary Atresia, and by the time she reached us her opportunity for intervention had slipped away. Now, this story is not unique. Children of color are disproportionately impacted by delayed diagnosis, often referred to specialists after the critical window for intervention has closed.

They then face a future that includes either a late-stage intervention, or liver transplant. The transplantation isn't a cure for biliary atresia. It's a complex lifelong management plan that introduces new

risk and challenges, such as immunosuppression, infections, possible re-transplantation, and elevated risks of certain cancers.

The only effective treatment for Biliary Atresia is a surgery called Kasai procedure. But to have the best chance of working it needs to be done within the first four weeks of life. After this window, the effectiveness drops, leading many children down towards the liver transplantation.

The only signs in this critical period are jaundice and pale stools. And they are often missed, or even dismissed. There is a solution that can prevent these delays. A simple, direct bilirubin test added to the total bilirubin that most newborn nurseries already perform could be the answer.

This isn't a burdensome addition, and doesn't require any extra blood or complex new procedure. It's what we call the point of care screening, a method that’s already established for conditions of congenital

heart defects and hearing tests. Newborns across the nation already undergo total bilirubin testing, either via serum or transcutaneous methods to assess for hyperbilirubinemia.

By fractionating, or splitting it, that existing test to include direct bilirubin we can screen for Biliary Atresia with minimal disruption to the current practices. Direct bilirubin screening is not only simple and accessible, its effective. It has a high sensitivity and specificity, with a low rate of false positives.

My experience with missed BA patients have led me to implement screening for this disease in the third largest hospital in Texas, and at the largest birthing hospitals in the Bay area, where I'm currently based. With plans to expand to three more institutions across the U.S.

Our protocol is straightforward. We test at 24 to 48 hours of life, when they're already getting the

newborn screening, and possibly their total bilirubin checked with no extra blood. And if the direct bilirubin is elevated, we retest at two weeks of life. If it's still elevated, we refer to GAI. Giving these children a chance to undergo the Kasai procedure early, and avoid the burdens of a liver transplant.

I am here before you today not only as a physician, but as someone who has seen these families and children, families who love their children deeply, and trust the health care system to guide them. Biliary Atresia screening is safe, improved, and a feasible addition to the newborn panel. It could prevent many families from needing to navigate the challenges of late-stage diagnosis, or lifelong management of the transplant complications.

The need is clear. With a simple change, we can change we can save lives, improve outcomes, and give children a healthier future. I urge the Committee to consider the profound impact of adding Biliary

Atresia to the newborn screening panel. Chairman Calonge, I'm very thankful for you and the Committee's review of their nomination package this year.

We look forward to the continued work with you, so that Biliary Atresia can be added to the RUSP in a way that is sensible for hospitals, and hopeful for babies. Thank you very much.

CHAIR CALONGE: Thanks, Tebyan, appreciate it. Next we have Bo Hoon Lee.

DR. LEE: Hi. And thank you for the opportunity to speak today in support of Duchenne Muscular Dystrophy, currently under consideration by the Committee. My name is Dr. Bo Lee. I am a child neurologist at the University of Rochester, where I currently direct the Pompe and Spinal Muscular Atrophy newborn screening follow-up clinics, and co direct the pediatric neuromuscular program.

As such, I have experienced how transformative newborn screening can be for patients

that I care for. We're a certified Duchenne care center, and follow approximately 140 patients with Duchenne and Becker Muscular Dystrophy. I am lucky enough to live in New York State, where there's already legislation for DMD newborn screening to start.

And once it does, I'll direct our New York State designated neuromuscular specialty care center that will receive referrals for DMD at my institution. Additionally, I am interested in leading a clinical and research consortium in New York, that will work towards characterizing the early natural history and standardizing the clinical care in babies with Duchenne Muscular Dystrophy.

As you've heard before, data from MD Starnet and others have shown, that despite over three decades of broad efforts to improve clinical identification with CK based screening in infants and toddlers, the delay to diagnosis persists, with an average age of diagnosis at nearly five years.

You keep hearing about the diagnostic delay as it's a frustrating and all too common situation that those of us who see and treat Duchenne encounter. However, in the most recent past that frustration is further compounded by the fact that we have a growing number of treatments that would have benefited the boys.

In the past year alone I've met and diagnosed multiple children with DMD several years after clear, clinical symptom onset, including a boy who had already entered the late ambulatory phase of the disorder, and came to me never having had a CK checked. This is unacceptable. The equity injustice impact alone of DMD screening will be significant, as multiple studies have already demonstrated that children of underserved minority groups are disproportionately affected by the diagnostic delay.

In a study out of UVM, the delay was also more pronounced in boys with co-occurring neurocognitive diagnoses like autism. I strongly believe that newborn

screening will relieve the differences in time to diagnosis against these disadvantaged groups. Importantly, in 2024 DMD is a treatable disease, and earlier treatment is better.

The number of therapeutic interventions available for our patients has grown significantly, and continues to expand. We have multiple gene-based drugs, and multiple drugs with down tree mechanisms of action that have been FDA approved for Duchenne. This includes Elevidys gene therapy, which is currently approved for boys older than four years of age.

And even with the expanded approval allowing treatment in boys past their sixth birthday, by the current average age of diagnosis many are still being watched through the complicated and stressful decision-making process of obtaining approval and access to therapies like Elevidys.

When the diagnosis is delayed, there is irreversible muscle damage that has already occurred.

And the opportunity to stabilize the progressive muscle fiber loss with corticosteroids and other disease modifying drugs as early as possible is already narrowed. Furthermore, an early diagnosis provides actual knowledge beyond pharmacologic intervention.

We should be careful not to undervalue the benefit of earlier access to support services. Early implementation of appropriate diagnosis guided ancillary therapies and school preparedness in these young children. This benefit extends not just for the early differences in motor performance, but also in screening for, and intervening on, the highly coincident language and speech delays, and spectrum of neurobehavioral diagnoses that we see in DMD, like autism.

For these reasons, and many others, I believe that it's time for DMD newborn screening, and I'd like to thank the Committee for the time to speak, and for your continued consideration in moving newborn screening forward for Duchenne.

CHAIR CALONGE: Thank you for your comments. I appreciate it. I'd like to ask Ashley Stimac to present next.

MS. STIMAC: Hi there. Good afternoon. I'm Ashley Stimac, this is my husband, Tyler, he's joining us as well. And I'm here as an advocate, a labor and delivery and NICU nurse, and the parent to urge the addition to Duchenne to the recommended uniform screening panel for RUSP. Let me introduce you to my son, Connor. Connor's journey, like so many with Duchenne, highlights the serious consequences at the late diagnosis.

As parents we noticed Connor was missing key milestones. Despite being taken to multiple pediatricians and neurologists, we were told repeatedly that since his cognitive he was cognitively fine, there was no need for further testing. His gross motor delays were downplayed. Invaluable time was slipping away. It took our insistence as parents, and me as a

nurse to demand these labs. I actually had to order the labs myself, and request them from the pediatrician.

The results came back, and they showed elevated liver enzymes, an indication that expedited our access to the genetics department. Prior to that, our genetics department was making us have a one year wait list to get in to see them. And we feel so fortunate that Connor was diagnosed when he was.

One especially close call involves surgery Connor had scheduled. Had we not discovered his condition just a week earlier, the use of general anesthesia could have had a devastating outcome, given Duchenne's unique risks. Early knowledge of Duchenne can mean the difference between safe medical care, and preventable tragedy.

Thanks to his diagnosis, Connor now receives early intervention. He is in aquatic therapy, physical therapy, OT, and physical therapy. He is also able to start steroids, a treatment that helps preserve his

muscle function. And with advancements in medicine, we're hopeful that he may soon benefit from other therapies currently in clinical trial.

Early detection offers more benefits. For families, it provides precious time to process a lifechanging diagnosis, allowing thoughtful decisions rather than rush choices. It means opportunity to adjust insurance claims to cover specific needs in advance, rather than reacting mid-year, which often adds unexpected stress and expense.

Early diagnosis also prevents the years of missed diagnosis that many families face, sparing them unnecessary medical costs, endless appointments, and the frustration that ripples through every aspect of the family life. It allows for financial assistance that can be a lengthy process, and often results in reduced medical costs overall.

With early awareness, families can make important life decisions like purchasing single story

homes that's accessible for wheelchairs, and accessible schools, or planning for vehicles that can accommodate a wheelchair. Decisions that become much more costly if made reactively down the road.

Adding Duchenne to the RUSP would empower families to make informed decisions early on, giving children like Connor the best possible chance at a higher quality of life. Please make sure that no other families endure the endless delays and hardships we faced. We have the power to change the course for thousands of children. Thank you.

CHAIR CALONGE: Thank you, Ashley. Now, Katherine Anderson?

MS. ANDERSON: Hi there. Good afternoon Thank you Chairman Calonge, and the Members of the ACHDNC for the opportunity to speak today. My name is Katherine Anderson, and I'm the community resource manager at Parent Project Muscular Dystrophy.

I'll be sharing an update to PPMD's work to

quantify the benefit of early treatment in Duchenne. Duchenne is progressive and systemic, gradually robbing children of the mobility to play tag, the arm strength to hug their families, and the pulmonary strength to sing their favorite songs.

There's no cure yet, but Duchenne is treatable. Boys often first present with speech and developmental delays, for which early interventions ensure the best possible outcomes. And we now have eight FDA approved medications that are specific to Duchenne, giving patients more quality years of walking with healthy hearts and lungs.

Duchenne is genetic, but in about a third of cases, it arises from a random genetic variant. This means that every American expecting a child could face this journey, and the risk of a long, agonizing path of uncertainty before a diagnosis is even confirmed. Families often notice delays by age two, but the average age of diagnosis is still around age five, and many are

diagnosed even later, when their muscles are already in severe decline.

At PPMD I meet many families with newly diagnosed children, and the story that I repeatedly hear from families of children nearing age ten is that I knew something was wrong, and I pushed for answers in every way I could, and now I've lost so much time.

These families do everything right, and still spend years fighting through unnecessary tests, costly specialist visits, or even damaging therapies, all while watching their children stagnate and regress without appropriate treatment. This is particularly pronounced for families of color, who face more disparities with longer paths to diagnosis.

All families deserve the opportunity that newborn screening provides to get the right therapies at the right time for them, including securing care for developmental delays, and taking advantage of the seven life-changing FDA approved treatments for babies two or

younger.

There is tremendous power in your hands to change the story. Newborn screening is the only tool that will empower all families to make fully informed treatment decisions while their children still have muscle to preserve. PPMD is leading an initiative to promote research on the impact of early care. Four of our certified Duchenne care centers are submitting data for a pooled cohort of boys treated with steroids.

The study will assess whether treatment before age four yields better outcomes compared to later treatment. The analysis will include variables such as the participant variance, steroid schedule, and other Duchenne treatments. On March 5, 2025, PPMD will host a virtual symposium focused on the early treatment in Duchenne.

The results from the collaborative study will be presented alongside insights from other experts in DMD care. Let's bridge our decades long work improving

care with the advancements we have in diagnostics, treatment, and long-term follow-up. Together we can change the narrative of Duchenne to one of hope, in which parents have the clarity and assurance of early diagnosis to make timely decisions for their children's treatment.

Thank you to the Committee for your continued consideration of Duchenne into the RUSP.

CHAIR CALONGE: Thank you, Katherine. Now I'd like to turn to Christine Tippett.

MS. TIPPETT: Hi. Thank you so much for finding me. My name is Christine Tippett. I'm here to advocate on behalf of adding Morquio to the RUSP. My family and I live in Littleton, Colorado. Our 12 year old son, Cooper, was born September 12, 2012, a healthy baby boy. Our world crumbled 17 months later when we received Cooper's diagnosis of Morquio syndrome.

Our diagnostic journey was relatively short at seven months, but a diagnosis at birth would have

made a world of difference. The thing I remember about diagnosis was the eight days when we didn't know what was happening, when we were told, "We think it's an MPS, but don't Google it." We were confused and scared.

The pediatrician made calls to get us into the Metabolic Clinic ASAP. I sensed an urgency that scared me. The emotional and physical effects of the stress this puts on a family is indescribable. It's a terribly dark time. A diagnosis at birth would have come as a surprise, but I'd prefer it over a journey which felt like watching a train approach as we were tied to the tracks.

If at Cooper's birth we were given a diagnosis, we would have been 17 months faster to not only life altering ERT, but the equally important Morquio community. I can tell you from experience you can't find anyone who remotely understands what you're going through, while sobbing in the women's room at Children's Hospital.

Cooper himself will tell you how important infusion day is. How he feels tired if he misses infusion for more than a week. Cooper's first grade teacher shared with me that she could tell which day Cooper had infusion because the following day he was super fast on the playground, a big difference from the other school days.

A month after diagnosis we found our community, 1,500 miles away, a listening ear on a confident, compassionate, knowledgeable mom of a Morquio daughter. My aunt found Stephanie sharing her daughter's journey on the internet. Families dealing with a rare disease desperately need community. They need someone who truly hears and sees them. They need a seasoned parent who can tell you who to call at which doctor to get answers.

A comrade at arms to send you to the National MPS Society to make more connections and find resources. Parents need a community who can share their

experiences, listen to their fears, and hold their hand during life changing moments. I know that an earlier diagnosis wouldn't have given my 38 inch tall sports crazed boy the chance he wants to play in the National Hockey League, but an earlier diagnosis would have given his family a better, more educated start for his and our future.

For all our kids, all we want is the chance to do the very best. A diagnosis at birth gives kids with Morquio a chance for the very best. Here is Cooper meeting his hero, Colorado Avalanche's Cale Makar this week. Where's Cooper? Oh, he's the short one. You'll find him, he's there.

The photo certainly is one for the highlight reel. I'm hoping the next part of the highlight reel is seeing kids with Morquio like Cooper diagnosed at birth. Lastly, here's Cooper when he did find his community. Two boys sharing his same journey with the same diagnosis. So thank you very much for your time today.

CHAIR CALONGE: Thank you, Christine. Thanks to all, especially parents and advocates for presenting today, and sharing your stories. These are very important for the Committee to participate in, to hear, to help understand the importance of the work that we do here on the Advisory Committee.

I also want to appreciate the work from the clinicians who dedicate their lives to taking care of these children with rare diseases, and trying to alter their health and life trajectory. With that I will close the public comments period, and we'll move on in the agenda.

Family Outcomes of Newborn Screening: Project Update

CHAIR CALONGE: Next up we're going to hear from Drs. Don Bailey and Elizabeth Reynolds from RTI International. They will provide an update on their work, on assessing domains of family outcomes, and considering what should be measured for quality of life

for both individuals and families identified with genetic conditions through newborn screening.

HRSA provided funding to support RTI's project. This work is a direct response to the things the Committee has heard from various stakeholders, and again today, as in today, during public comments. It also aligns with HRSA's Blueprint for Change, a national framework for a system of services for children and youth with special health care needs.

One of the four critical areas of the framework is quality of life and well-being. To introduce our speakers, Dr. Don Bailey is a Distinguished Fellow at RTI International, where he's a member of RTI's genomic and translational research center. He has an extensive record of publications on a variety of topics related to disability, early identification, early intervention, newborn screening, and family support.

He is a Senior Science Advisor for Early

Check, the statewide research project to help prepare newborn screening for new conditions and new technologies, with a current focus on whole genome sequencing. He also leads this project funded by HRSA to identify and develop ways to assess family outcomes of newborn screening.

From 2011 to 2017, he served as a voting Member on the U.S. Department of Health and Human Services Advisory Committee on Heritable Disorders in Newborns and Children. I will go ahead and introduce Dr. Elizabeth Reynolds, who is Manager and Research Public Health Analyst in the genomic, ethic and translational research for G-E-T. or GET programs, at RTI International where her interests include rare and genetic diseases, patient registries, and early developmental outcomes.

She is leading a project examining links between newborn screening and early intervention, developing an assessment to evaluate family outcomes

after genetic diagnoses, and creating a tool to integrate electronic health records in the patient registry. She's also the founder and Executive Director of the Champ Foundation, a patient advocacy group with a mission to support research, find treatment and a cure for single large scale mitochondrial DNA deletions like Pearson Syndrome.

Welcome to both Doctors Bailey and Reynolds, and I'll turn things over to you Don.

DR. BAILEY: Can you hear me okay?

CHAIR CALONGE: Yes.

DR. BAILEY: Great. Thanks for that introduction, and thanks for the opportunity to provide an update today to the Committee. I just want to start by saying how inspiring it is to hear the stories that families share with the Committee. We hear these stories every meeting, and they really help shape our perspectives, and ground us on what's really important, and why we do newborn screening.

As all of you know newborn screening focuses primarily on child outcomes, but many of us believe that family outcomes are also important, and so this is the focus of the work that we're doing, and we're very appreciative of HRSA for supporting this work. Next slide please.

So, you know, we gave quite a bit of background to this work in a previous Committee meeting, so I won't go through all that again. I'll just say that this is grounded in some early work we did many years ago with early intervention, where we were looking at how families benefit from, and what are their outcomes from early intervention programs for children with developmental disabilities.

And so this extends and expands that work to a new context of newborn screening. So, obviously we all know that families can benefit from newborn screening, but what are those benefits? We don't know a lot about them. We can speculate on them, we can

describe them, we can hear stories about them, but we don't have a good way to measure.

And so, we did develop a measurement tool, a family outcome survey, a family outcome scale as a part of early intervention, and we're now going to be doing the same thing with in the context of newborn screening. So this project is the first step in developing such a tool. So, as you can see from this graph we've been or this figure, we've been spending quite a bit of time getting input from a variety of different groups.

And if we can go to the next slide I'm going to give you a high level view of what we've done so far, and then Dr. Reynolds will give you more detail on each one of these steps. So, the first thing we did was establish a fantastic expert advisory committee. We've engaged the regional genetic networks to get input.

We conducted a major literature review with our focus groups, and all of this was designed to help

us develop an initial set of what we call outcome domains. Ultimately, we'll have a tool with a number of different items on it, but those items need to link back to particular domains, and that's where we want to start is understanding what are the chunks, what are the chunks of the outcomes that would be important to examine as a part of newborn screening?

So how does all of this work, and based on it, and our previous work we now drafted an initial set of outcome domains. We have shared those with a number of groups already, and we are in the process now of getting ready to revise those outcome domains, after which we will distribute them widely for another round of input.

This will be a very large-scale effort Elizabeth will describe. We're also preparing, and will publish individually a manuscript on describing how we got to these outcomes. These will be important grounding for our work, and then we'll be moving from

that into developing a scale. So, I'm going to turn it over now to Dr. Reynolds, who will share more details about each of these activities.

And we know you have a very busy schedule, so we'll go through these pretty quickly, and look forward to a more detailed presentation in a subsequent meeting.

DR. REYNOLDS: Okay. Thank you very much, Don. You can please go to the next slide. Okay, great. So, now as Don mentioned, I'm going to be providing some specific details about the methods that we use to get to this point. And so, here you can see this is our team of expert advisors that we, you know, set out with the intention to include participants with a diverse background and experience to inform our overall project objectives.

And ultimately, this is our 13 member advisory committee. I think there is some people here on this call today from the Committee, and it included patient advocates, patient advocacy groups, parents of

children who were identified through newborn screening, newborn screening laboratory and follow-up directors, clinicians, genetic counselors, APHL representatives, and family researchers.

Our advisory committee met three times over the last seven months. The first meeting was in March, and we focused on our project overview and goals. The second meeting was in May, and this was where we had our presentations from the regional genetic networks that I will discuss a little bit more about in a minute, and we had our final meeting in September, and this was the first round of feedback and reviewing that we had on our set of drafted outcomes. Next slide please.

The regional genetic networks were originally funded by HRSA to develop and support an infrastructure system relating to genetic services, and there are seven RGNs, and each receives supplemental funding from HRSA to identify family outcomes after newborn screening. And to fulfill this requirement, the RGNs collected the

background of families using a variety of different methods, including listening sessions, focus groups and surveys.

And given their unique access to these families, and our aligned priorities, we invited each of the directors of the RGNs to share their findings at our second advisory committee. And we asked them to present using a standardized template, and share about the specific activities they use to solicit feedback, describe the high level characteristics of the participants, and identify the five most important outcomes that families brought up following a newborn screening diagnosis.

We had four RGNs accept this invitation, including NYMAC, New English Regional Genetic Network, the Mountain States Network, and the Heartlands, and they shared their results with our advisory committee. Go to the next slide please.

And as Don mentioned, also we conducted a

systematic literature review of articles related to family outcomes and newborn screening. And specifically, we used these search terms, and we identified 149 articles to review. For each we conducted a thematic analysis using some of our pre-identified themes, and these pre-identified themes included access to information, access and use of high quality services, family's ability and skills to meet the needs of their child, financial needs, social needs, and other, and we categorized findings from each of these articles based on their themes, and then we identified sub-themes.

So for one example we had, you know, our pre-identified theme of access to information, and a sub-theme that we learned was that families, even after getting information from their clinicians, there was a need for families to do their own research using online sources, patient advocacy foundations, and connecting with other families on social media groups. Next slide

please.

Can you click it one more time? I'm sorry, keep going. I didn't realize there was yeah, I think that's everything. Okay. Thank you. So, we conducted three focus groups for parents and patient advocates, and prior to these focus groups we asked the parents to also complete a journey mapping activity. And this activity presented parents a series of sequential text boxes, and for each box they were asked to describe a key event in their family's journey, or their child's journey.

And they provided details like the age of the child, what was challenging about the event, and what made things worse, and also what made things better, and what went well, and then what would have been an ideal outcome from that event. And following those, reviewing those journey mapping activities we ultimately had three focus groups, so we had 14 participants total.

The first two focus groups had parents, and

the second focus group had patient advocates. The moderator guided the discussion using questions again from those pre-identified themes that we had identified in the literature review, although what we had identified using the journey mapping activity, so these themes now were the access to information, access and use of high quality services, the ability to meet the needs of the child, financial needs and social supports.

And after the first parent session we also added additional themes, including quality of life and mental health of parents. All right, next slide please. Sorry. Here we go. Okay. So, after we are data gathering with our literature review, our regional genetic network outreach, and these focus groups, we revisited our teams development of the family outcomes scale for early intervention.

Don had mentioned this in the beginning that our team had developed this specifically for early intervention. And despite our known differences between

EI and newborn screening, this framework provided a starting point to map our themes into actual outcomes, to be able to assess family outcomes. Next slide please.

So, here are the current draft outcomes of newborn screening, and we'll reiterate that these are in the draft form. We started soliciting feedback from these, and we're hoping to get feedback again today, and I'll read them out loud. So, our outcome one is that families understand their child's diagnosis and treatment options.

Outcome two is that families access high quality medical care, treatments and services. Outcome three is that families navigate health care and service systems, and advocate for their child. Outcome four is families manage the day-to-day needs of their child in the home environment. Outcome five is families maintain emotional well-being, and have support systems, and outcome six is families achieve optimal family

functioning.

Next slide please. And so, I'm going to just pull out this first outcome as a specific example. So, our outcome is that families should understand their child's diagnosis and treatment options. And below in the bullets are some specific examples of evidence that this outcome might be achieved, so families understand how the condition impacts their child’s health and development now and over time.

Families are able to evaluate conflicting, incomplete and complex information, and families know specific next steps for treatment and care. And so, now we're developing these types of examples for evidence for each of these draft outcomes. Next slide.

And after we do some revisions on these outcomes, as Don also mentioned, our next step is to release this public survey to get overall feedback on all of these draft domains. And this survey will be online, and will be intended for anyone that's involved

or affected by newborn screening.

And for each draft outcome, we will ask things about whether the participant thinks how important they think it is to measure, whether they think the outcome is clearly written, and whether they have any ideas or concepts that are critical to be measured when assessing this outcome.

And the last question we'll be asking if they think that we are missing any family outcomes, or any domains that they don't think are reflected in this initial draft. And so, we are hoping to have a survey that goes live over the next few weeks, so if you get an email from us, we hope you take the survey, and also share it with your networks. Next slide please.

So, wrapping up, I've identified our steps to how we got to this point, and describe our efforts to develop a scale to assess family outcomes after newborn screening. We are going to now revise these outcomes based on the feedback that we've already gotten, and

also that we plan to get in the future, and then we will publish our findings and where we are to this point.

All right, I have the final slide to say thank you very much, and I think that Don and I are now available to answer any questions that you have.

DR. BAILEY: Thanks, Elizabeth, and if I could just make a few final comments, Dr. Calonge. In our last meeting we made a distinction between outcomes and satisfaction, and we think this is an important distinction, of course. It's very important for families to be satisfied with services, both during newborn screening with the program itself, but in subsequent treatment services, genetic counseling, and so forth.

And so, it's an important thing to document. The satisfaction is only one part of a broader understanding of what newborn screening means to families, and so what we're very interested in is specific outcomes. Now, you can say outcomes from

newborn screening to outcomes after newborn screening, outcomes as a result of newborn screening.

And it's hard to link them necessarily directly to newborn screening because so much happens, right, after the screening itself. Especially if you wanted to use an instrument like this two or three years post screening. So, you know, a better title might be family outcomes, outcomes for families who have had children identified through newborn screening.

We want these to be very practical outcomes, functional things that actually could identify areas that need strengthening and follow-up, support for children and for families. Also, we think it could help serve as a longitudinal tool to look at how families change over time, and what factors might influence family change.

So, we're very excited about this work. These will not be items that, you know, a professional would sit down and rate a family on, these would be

family's perceptions of their outcomes and their benefits, and so we're really very hopeful that ultimately we'll have a useful tool that could fill a variety of research and program improvement goals, but thanks very much. I'm glad to answer any questions.

CHAIR CALONGE: I appreciate it. And thanks to both of you for coming and sharing where you're at in the current project and promised what you found. I know we are all looking forward to what we continue to learn from your work, and the use of your tools. We look forward to accepting the benefits associated with early detection and treatment.

Committee Discussion

CHAIR CALONGE: I'd like to open the meeting to comments and questions, starting with Committee Members, and then turning to our colleagues, our Organizational reps. Jeff?

DR. BROSCO: Thanks again for this

presentation, and just to connect with the different things that have happened today. So, you know, we started earlier today talking about the involvement of families and patients and research, and so one of the things as Don mentioned, is that you could use this tool as an outcome in research, right, across a whole bunch of different commissions.

We at HRSA are not very much into research. That's not our main mission, right? Although we have some projects like this with RTI. We are much more into making sure the system of care works for every single child, and so we support state newborn screening programs, not just to make sure that the conditions on the RUSP can actually be screened for, but we're now trying to turn toward well, what happens afterwards?

And as Don pointed out, this is not really just an outcome for families of newborn screening, but everything that happens afterwards. With the principle that it's no good to screen for something if a family is

not able to get the treatment they need, and the resources they need to get things done for their kids.

So, we're hoping that as this becomes part of the system of care, so we're measuring our health care system not just on whether a child had a well visit, or they had a vaccine, which is commonly how we measure our health care system. We also are looking at what really mattered to families, then we would be able to do a continuous quality improvement approach that really made sure the kids were thriving.

So, this is a critical set of works that Elizabeth and Don and their team are working on, and we really want to thank the Committee for really driving this work early on, and I think it might have been Natasha Bonhomme who said we really need to pay attention to what families need if we want to make sure the system is working right, so thank you all.

CHAIR CALONGE: Thanks, Jeff. Ash?

DR. LAL: Yes, thank you for the

presentation. A really important aspect of their work. The question I had is that I think both outcomes and families can be viewed in possibly two ways. One is whether there are answers, or there are facilities that are available that the family has to be accessing, or perhaps there are the system deficiencies which produce less than an optimal outcome for families.

For example, looking at the outcome three that families navigate health care and service systems and advocate for their child. Is that so that means partly, well it will all depend actually on whether the health system has built in certain features like a navigator, a patient navigator for rare diseases, and where multi-assist, multi-specialty care can be coordinated in some way.

So, is there would your surveys allow for some of the distinctions so that that could inform HRSA, and the health systems could improve?

DR. REYNOLDS: Okay. Yeah. I'll just speak

to the difference between outcome two and outcome three, and I think that's something that we have now heard from different from feedback from different groups. And so, I think that we're envisioning outcome two, which is family's access, high quality medical care, and that to me would include access to care coordination, so families have care coordination at the hospitals, and the care coordination is helping them do outcome number three, which is the ability to navigate and access those services.

But that is something that came up, I think, in almost all of our focus groups, and in the presentation from our regional genetic networks that families, even with care coordination, families have to have they have to advocate for their kids to be seen at different specialist centers, and they have to kind of be able to work through the system.

So, I think that how we're seeing it right now that it's important to keep both outcomes, but that

is something that, you know, we might be able to merge, or think about whether they should be merged for those two outcomes.

DR. BAILEY: That's a really important question, Ash. Thank you very much. And the tricky distinction that we're trying to make here is it seems like it's a fine line to a certain extent, but it's important. So, we're not going to be asking are there systems of care available for families for a particular disorder, or specialized treatment center because that's a system.

What we want to know is about the family themselves, so an example of flipping that around is that families are confident in their ability to find and access existing services. So, it's not the fact and then you can start asking questions like well, if there are only two, you know, treatment centers in the county for one condition versus you know, 20 for another condition, do you have different family outcomes in that

set of circumstances?

So, that's a little bit of a distinction between what we're trying to accomplish here. It's hard sometimes to disentangle those things, but we've done it before, and so we'll be using lots of feedback mechanisms to help to try to do that again. Hopefully that helps.

CHAIR CALONGE: Natasha?

MS. BONHOMME: Hi. Natasha Bonhomme, Genetic Alliance. This builds on the conversation we're already having. You know, where do you see is the appropriate place, and maybe this is going to inform by the work done in early intervention, to have that I guess you could call it a critical look at the system? You know, I think these outcomes are really good, and I worry that someone either intentionally, or unintentionally would read the outcomes, and the onus and responsibility is on the families when there are certain things that I'm looking at I took a screenshot of the outcomes, you

know.

You know, what part of outcome one, let's say you know, families understanding their child's diagnosis and treatment options can we tie to the families, and what part of that do we tie to the system? And just if you could just speak a little bit more to how you see parsing that out, where that would live? Maybe that lives in a different phase of this project, or it lives in a different place. That would be helpful for me, thanks.

DR. REYNOLDS: Yeah. I mean I think that it's a really important question, and I think it also depends on the either the research question or the purpose, and the timing of when this tool is used. I think specific for, you know, outcome one that you brought up, so families understanding.

We had a really great pediatrician on our expert advisory panel, and she was saying that if she was reading the, you know, family's responses, and that

was, you know, over and over we were learning that the families were not getting the information that they needed from their doctors, and they were going to, you know, the advocacy groups, or Facebook groups to find out that information that they needed.

Like what can she do differently to support those families? So, I think that we're hoping that it does not fall on the family to say this is because, you know, it is the responsibility of the family to understand the medical care and the treatment options within the first couple weeks of learning their diagnosis, but what can we do if we're, you know, if families are not understanding?

Like how can the pediatrician then say okay, what can I do differently when we share that information back?

MS. BONHOMME: Yeah, and I just want to add into that. I think to me too it's also hard to understand what success looks like, and maybe that is,

you know, success looks like X, Y, Z, depending on if this is being used in a research context, or being used in a different context.

But, you know, because even then I don't sure yes, a pediatrician should be able to help a family understand, but going to an advocacy group isn't necessarily a fail, right? There is success in that, and so how do we where and how do we construct that so we may not necessarily be saying oh, that's a good outcome, or a bad outcome.

It's just these are this is what's happening, this is the reality, how do we support the best possible not to say satisfaction, so I don't want to say experience, but you know, the best possible outcomes for these families, so thanks.

DR. BAILEY: And just to further add to that, so you know, we don't see this tool as being as meeting every, you know, measurement need in the system. It fills a gap for where there's nothing available right

now, but there will certainly be, you know, tools to look at it. Other people, there are existing tools to look at best acts of the system, you know, how the family centered program is, timeliness of things, et cetera.

And this would be one way to look at whether those things make a difference ultimately, in family outcomes. Really an important point is we don't want this to come across as in a way that families would feel judged, or that they would feel uncomfortable saying you know, I don't really know how to access my child and get the right kind of services for my child.

So, ideally we would be doing that in a more sensitive one-on-one interview or discussion with families, but we're hoping to have a scale that would be used an instrument that would be useful at large scale. And so, how this is presented, introductions to it are going to be really important, to make sure that we just we want to find out information that would help

us improve the system to better meet your needs.

And the only way we can do that is to have you provide this information for us.

DR. BROSCO: And this is Jeff, maybe I can give a use case example to help Natasha and others see how this might be used. So you may remember a year or two ago we had the Connecticut newborn screening folks present, and we'll have a follow-up. And they connected their newborn screening results to Connecticut Children's Hospital, and it gets built into the electronic health record.

It's basically used also at Yale, so there's two hospitals that take care of most of the kids. And so for things like sickle cell disease and hypothyroid and a few other conditions, they now have a population based approach where they can look at every single child identified by newborn screening, and those conditions, and say which of them are meeting clinical guidelines.

And they've demonstrated over a couple of

years that by using that, not just at the individual level, but at the clinic level, and at the statewide public health level, they've increased their adherence to clinical guidelines from about 60% to above 90%.

Really extraordinary. It's a great example of how the system is working. They're currently sort of sending out the families ahead of visits, a thing that they put together that says how are you doing? And what we're hoping is once the RTI team has developed a measure that's sort of built up and based on research, that we'd be able to use that.

And they would say we would use that instead. Say what is working well on the system and what isn't. And so, it would be a continuous quality improvement approach. Absolutely not to blame families, but to say what is it we're doing that's working, what is it we're doing that's not working, and how do we make that better. So that's one of the ways we could see this being used in a system of care setting.

CHAIR CALONGE: Thanks, Jeff. Amy?

DR. GAVIGLIO: Yeah. I just wanted to reiterate some of the comments I think, especially some of the last comments from Dr. Bailey, and some follow-up on Dr. Lal's question that we as, I think the expert advisory committee, I think really struggled with how to determine outcomes as a true result of the newborn screening process versus outcomes we see simply as a result of a health care system that's currently not set up to appropriately care for patients and families with rare diseases, no matter the modality of detection.

And so, I think this will be a continued important consideration as we think about things like outcomes and harms, you know, understanding that dealing with a chronic condition even when detected early, is still not easy, and there will remain issues with access and trauma across that lifespan, and truly until we fundamentally change our health care system, which is unlikely to happen any time soon.

I don't think we can or should expect that newborn screening will necessarily result in kind of the successful achievement of all of those outcomes. And so, I'm wondering if we need to also be thinking about what a control group will look like, you know, what should we be comparing to? Are we comparing to those who went through a diagnostic odyssey, and had a clinical diagnosis?

Are we comparing to those who have common complex diseases? Kind of what is our baseline that we would be comparing outcomes to in order to determine success?

DR. BAILEY: Well, that's a really good question, Amy. You know I think part of me says that's really not what we're trying to do. We're trying to say we want to know where families are after newborn screening because knowing that in and of itself will help us know where and how to improve the system, and help us know whether we're being successful in a variety

of aspects of what we're doing.

And obviously, and you're right. There are going to be other things that we're not going to be tapping here, both characteristics of the system, but also some of the negative things that this Committee has considered in the past, like parent anxiety about uncertainty.

You know, families, you know, stress and parenting is stressful in trying to find good services. So those are their tools available to measure those kinds of things, and what we're trying to do here is measure, you know, benefit, the positive things that could happen, and whether those benefits are achieved or not.

And so, we'll leave it up to we'll think about your question about a control group. But obviously, there's not going to be kind of a random assignment, randomly assigned control groups. There could be some historical groups that we could take a

look at. You could look at a group of families. I'm sure Mike Hu would be able to give us some examples of families that have children with MPS that were identified late, and the damage of the children identified early, and examine some outcomes in each of those situations.

It wouldn't really be a totally fair comparison, but there are interesting things that we could do like that. You know, Don, I'm just intrigued by the juxtaposition of this presentation and the promise that you worked with before, and like the PCORI presentation, and just wondered how the tool and the assessment could be something they were aware of as they put together potential funding opportunities, especially in the rare disease and specifically newborn screening areas.

So, I just see this kind of outcome is exactly what PCORI was focused on, and I don't know how to make that link other than to say I hope you contact,

you know, the folks at PCORI and say we want to make sure you're aware of the work produced.

DR. BAILEY: Thanks Ned, and we will distribute information widely. We're really hoping to get a peer review publication in a high-quality journal, so that we'll have also a strong basis for sharing information, but you're right. So, clearly early descriptions of the activity and what we're trying to accomplish could actually and getting that information out to the writing sources that can inform what we're doing as well, so thanks very much.

CHAIR CALONGE: I appreciate it, and I really want to thank you both for coming and presented. Elizabeth, it was great hearing from you, and Don, it's always good hearing from you as well, and we look forward to the next presentation, which I think will bring us further still of things coming.

Metachromatic Leukodystrophy (MLD) Evidence-Based Review Update

CHAIR CALONGE: I know we've been going for a while. There's a break after the next session, so I hope folks can stick with us as we move into the next agenda item. You'll remember at our August meeting we voted to move Metachromatic Leukodystrophy to the evidence-based review, our evidence review group.

The ERG, evidence review group, is an external group that collects and reviews focused evidence on a nominated condition. The information they review may or may not have been included in the nomination package. As the approach this work is always do a confidence of literature, search of all available published evidence on which to inform our decision.

We'd like to have an update today. We're excited about that, and joining us for that update is Dr. Alex Kemper, the Lead of the ERG, and the Division Chief of Primary Care Pediatrics at Nationwide

Children's Hospital, Professor of Pediatrics at the Ohio State University College of Medicine. Dr. Kemper's research focuses on the delivery of preventative care services, including newborn screening, and since 2013 Dr. Kemper has also served as the deputy editor of pediatrics.

And you know, Alex, by the time I finish my tour of duty I bet I will be able to say that without reading it. Go ahead and take things over, thanks.

DR. KEMPER: Well, thank you very much. This is going to be a brief presentation today. The purposes is really two fold. One is just to update the Committee on the status of the review, and also talk a little bit about Metachromatic Leukodystrophy. So it's at the next meeting where we will have a longer amount of time to talk about where we are in terms of the evidence review, and present some of our modeling work in terms of what we would expect would happen if all newborns were screened for Metachromatic Leukodystrophy, and then it's

at the meeting after that that the vote occurs.

So again, the goal today is just to have a brief update meeting. Next slide please or presentation. Next slide please. This is just the list of our evidence review group the evidence review group around I'm really lucky to work with these dedicated individuals. Next slide please.

And then of course with each project we convene a technical expert panel of individuals who are knowledgeable, or who have lived experiences, a family member with the condition. We've had our first formal technical expert panel meeting already. Not everyone was able to come to that, but we're continuing to have conversations with those individuals who were not able to attend that meeting, and of course there are going to be many other technical expert panel meetings before the project is done.

Next slide please. So, I did just want to briefly provide an overview of Metachromatic

Leukodystrophy, mostly to level set with what we know about the condition. Next slide please. So, it's a lysosomal disorder that's associated with the deficiency of Arylsulfatase A, or ARSA is the name of the enzyme, it leads to the accumulation of sulfatides and that accumulation is- negatively impacts myelin leading to the neurologic findings associated with Metachromatic Leukodystrophy.

It is a progressive neurologic disorder that can lead to death when it's untreated. Reports of the birth prevalence varies regionally, and some of this may also have to do with how case detection occurs anywhere from about .16 per 100,000 live births upwards to 1.85 per 100,000 live births.

And again, we're still gathering information, and expect to have a more formal presentation of what we know about the birth prevalence at the next meeting. Next slide please. As the Committee knows, there are different phenotypes of Metachromatic Leukodystrophy,

ranging from late infantile to the early juvenile to late juvenile, and the adult phenotype.

What I would just like to highlight on this slide is that about 60% or so of the cases fall into the late infantile phenotype, and about 20% fall into the early juvenile phenotypes. And these are the most these individuals are the most really affected with the condition clearly, those with the late juvenile and the adult phenotype are negatively impacted by the condition. Next slide please.

In terms of the ARSA gene, there are over 1,100 variants of it described in ClinVar. What's interesting, and we've still diving into this, into the evidence is that unlike some of the other conditions that we've looked at, there's more information about which ones are likely to be pathogenic, or likely pathogenic, which of course is going to be important when it comes to issues of diagnosis and treatment. Next slide please.

The main targeted therapy for Metachromatic Leukodystrophy is gene therapy. Although it's true that the gene therapy was approved by the European Medicine Association in 2020, and the Food and Drug Administration in March of 2024, there's been a much longer history of evaluating individuals who have gotten this gene therapy with the oldest individual now more than a decade out from treatment.

I do want to dig into the treatment approach a little bit because it's different than some of the other gene therapies that we talk about. So first, what has to happen is that CD34 stem cells have to be harvested, and have to be retrieved from the individual. And then there's a viral vector that encodes for the ARSA gene that needs to be inserted into the stem cells. It's a process that takes, you know, six or eight weeks or so.

And then while this is ongoing the individual can undergo myeloablative conditioning that is preparing

the bone marrow for receiving back these stem cells by infusion. The gene therapy itself can be given as early as nine to 12 months of age, and the reason that it takes a little bit before the gene therapy can be given is because you have to wait for the infant to be big enough to appropriately harvest to retrieve and modify the stem cells.

So, as far as we can tell, and again, we're still in the evidence review process, so I just want to be sort of cautious and not drill into too many details, but there probably have been about 40 individuals who have gotten the gene therapy for Metachromatic Leukodystrophy, and have told you that at least one subject is now somewhere over 12 years of age. Next slide please.

So, the target of screening is really targeted to who is eligible for the gene therapy, so that includes the late infantile and early juvenile phenotypes. What's not a targeted screening because

it's not currently an indication for the gene therapy is the late onset phenotype, which is the delayed juvenile adult sub-types that I showed you on the previous slide.

There is also another rare condition called Saposin B Deficiency that leads to ARSA enzyme deficiency, but it's not targeted by the gene therapy, and it's not a target of screening, but in subsequent presentations you may hear me talk a little bit about it, and I just want to put it out there again that it's not a target of screening. Next slide please.

So, in terms of the approach to screening, next slide, there are really three tiers. So the first tier is measuring the sulfatides and the dried blood spot with liquid chromatography tandem mass spec the different sulfatides that could be measured. What I'm going to highlight is that if you use the C16:1-OH sulfatide, it really dramatically reduces the number of false positives, especially when you tie that to the second tier, which is the ARSA enzyme activity.

That's done that can be done in the same dried blood spot. Between the C16:1-OH and the ARSA enzyme activities, your false positive rate in terms of moving to the third tier, which is sequencing, is from what we can tell pretty close to zero. Again, we're still going through the evidence review process, but just to sort of give you the flavor.

In terms of the ARSA enzyme activity test, there is a screening test available, but there's a lot of work that's going on right now to make it more available, both within newborn screening labs, and in referral labs. Tier three again, I mentioned was sequencing, and diagnosis is based on confirmation of the elevated sulfatides. That can be done in whole blood or in urine, along with confirming low ARSA enzyme activity.

And then in terms of the molecular analysis, looking at the whether there are two severe pathogenic variants, or severe pathogenic variants, and

a pathogenic variant with some residual activity, those things really put you into the category that would benefit from the gene therapy.

I would like to point out that both with diagnosis and treatment there are clinical care guidelines that are available. Next slide please. So, I just want to touch a little bit with where we are in terms of current activity. Next slide.

So, we had the first technical expert panel. I talked about towards the end of October, we're continuing with key informant interviews. We've completed most of the first level review of articles, and there's something about 300 articles or so that they're going to go to the next tier with more formal data abstraction.

We've begun to think about the issues of modeling the impact of screening. We are looking for additional information, including from the gene therapy clinical trial that's going on in Italy, and looking for

in addition to the published reports that we have, unpublished information about outcomes from others treated with gene therapy.

There is some important screening activity that's going on right now, so in Germany there's a recent report in the New England Journal of Medicine, describing more than 100,000 newborns who were screened with three cases identified, including two with Metachromatic Leukodystrophy, who went on to receive gene therapy.

I have heard that there are another two infants that have been identified through that screening work, that again we need to trust or verify, get the information on it as well. There are lots of other pilot studies going on, including in Austria, in the U.K., and of course we're looking for other places within the United States.

Screen Plus in New York has been active with screening for Metachromatic Leukodystrophy, and there

are plans underway to transition that to the New York newborn screening program. There's also some preliminary work ongoing in other states, including Illinois, Minnesota, and Tennessee, all in a much sort of earlier stage of things, and of course there may be other newborn screening programs that are involved that we don't know about.

And then one of the important areas that we're trying to understand, and you know, I don't want to get into too much for the purposes of today because we're still gathering the data, but is around the availability of the second tier ARSA enzyme test in the United States, either for the newborn screening programs themselves, or as a send out laboratory.

This is an active area, and I suspect that when we present at the next advisory committee meeting, we'll have a lot more information about the status of things, so I don't want to sort of presume now about where things are going to be when we come again, and

just because it's such a fast-moving area.

Next slide please. So, let me just open it up for questions as well, in terms of if there are any questions about where we are now, particular areas that people want us to look into. I'm hesitant to dig too much into what we know about the benefits of early intervention, or screening and those kinds of things just because this is a work in progress.

Committee Discussion

CHAIR CALONGE: Appreciate the update, Alex. While it was an update it was pretty dense with information, and we appreciate kind of hearing where you are, and kind of where you're going. I wonder if there are any questions or comments starting with members, especially the 30 panel members that are participating on the Review Committee, if you're interested in making a statement or a comment that would be welcome, but not necessary.

DR. KEMPER: And I should say we just in terms of the liaisons we were just informed I haven't reached out to them yet to rope them in, so I don't want to put anybody on the spot.

CHAIR CALONGE: Ah, so they won't be able to provide any. So, I'll turn it open to the rest of the group. Alex, this is what happens when you say don't ask any questions.

DR. KEMPER: Don't ask any questions. Had I known that would work I would have like used that as a line on a regular basis.

CHAIR CALONGE: All right. Thank you so much. It's exciting. It's an exciting review. We appreciate the work so far, and we're really looking forward to the final presentation, discussion, and hopefully eventually the vote. And as always, my thanks to the ERG and all the folks that work with you.

Break

CHAIR CALONGE: And that brings us to our break, so why don't we stick with the concept of having a 15 minute break, and that would get us back here at it looks like 2:25. Is that correct? Yeah. 2:25 we'll go ahead, and as long as our next speakers are available, we can get started early, and go from there, so we'll see you in about 15 minutes, thanks.

(Break 2:10 p.m. 2:25 p.m.)

Laboratory Developed Tests

CHAIR CALONGE: We invite people to come back to the screens, turn your cameras back on to make sure I have a quorum, and we'll continue with the rest of our agenda for today. As people come back on, listening to Alex give his update on MLD, I'm just reminded that we are still working on DMD. We'll have more information for you in February, and that's all the updates I have for you at this point in time, but I want you to know

it's still in consideration, and still in the works.

It’s not dropped off, we're continuing to work, so I appreciate folks' patience and understanding the nominators who continue to work with HRSA staff, and this review group. That works. At this point we're going to turn to talking about laboratory developed tests.

In October of 2023, the Committee became aware of the final rule from the Food and Drug Administrations related to laboratory tests, or LDTs and we heard from several public health laboratories throughout the country that the impact of the ruling will have significant impact on their ability to screen for conditions that are already on the RUSP, and for future conditions that may be recommended to be added to the RUSP.

We invited a representative from Food and Drug Administration, the Center for Devices and Radiological Health to present to the Advisory Committee

on the final rule. They made us aware that there's pending litigation regarding the rule, and that FDA does not comment on pending litigation, and therefore, could not participate in the meeting in that capacity.

I will tell you that there is still the opportunity to provide comments on the final rule, if you look at LDT final rule on your browser it will get you to the LDT final rule @ FDA.HHS.gov where additional comments can be placed. So, given that we don't have our friends from FDA joining us to specifically talk about this issue, we've invited Peter Kyriacopoulos from APHL to provide us with more information on the final rule, and the phase out of policy for LDTs.

And then following that presentation we'll hear from Scott Shone, who is our Organizational representative for the Association of State and Territorial Health Officials, or ASTHO. He's going to talk about the impact of the final rule on state public health laboratories.

By way of introduction, Peter Kyriacopoulos is the Chief Policy Officer that serves as a Principle Public Policy Advisor to the Executive Director, and the Board of Directions of the Association of Public Health Laboratories. He's also a frequent consultant to senior CDC, HRSA, and FDA leadership on federal legislation and regulatory activities and issues.

Scott Shone is the Director of the North Carolina State Laboratory of Public Health. Prior to serving as the Director of North Carolina, Scott spent almost ten years at the New Jersey Department of Health as the Manager of the Newborn Screening Laboratory.

He's a member of the editorial board for the International Journal of Neonatal Screening. He's an Organization representative to our Committee, and representing ASTHO, and he's a President Elect for the Association of Public Health Laboratories. We are pleased to have both these experts with us today, although Scott had to be here. Scott I'm kidding,

thanks, and I'll hand things over if I could to Peter.

MR. KYRIACOPOULOS: Thank you very much, Mr. Chair, and Members of the Committee. I'm very happy to come back and talk and add a little bit more detail than my August presentation, and you can see here on this slide my name and the name of Amanda Cosser, who goes by Mandi, and does an awful lot of the thinking in this space for APHL.

So, the next slide there we go, is kind of a reminder of some things I've shared with the Committee already, so APHL, it is perhaps the only laboratory organization that is not opposing the Food and Drug Administration's efforts in the area of lab developed tests.

We are working very hard to develop and share useful information with FDA, so that they can accomplish their tasks, and again, I would remind you that FDA, like HRSA, like CDC, is a federal partner for APHL, and its member laboratories. The next slide is also a bit

of a refresher, some of the actions that have occurred, and it includes links to some of the comments that we have made not just on the final rule, but on the two draft guidance documents that FDA has put out.

And the reason that I want to remind the Committee about this is that we anticipate that there will be many more FDA guidance documents, and we are very interested in providing the information that FDA will find useful in the development of those guidance documents.

We've already spoken about the fact that we believe newborn screening tests require an immediate health response because so many states now have state law that says you must begin to implement a new disorder as soon as it hits the recommended uniform screening panel.

So, that is an issue that we have presented to FDA, and we will continue to discuss with them. The next slide provides an update on some of the activities

since we last spoke in August, so again, I think you've already seen we do have a position statement on the LDTs in general, and also comments on the proposed rule. We have been collecting comments from APHL member laboratories through our working very hard to understand what they need to do to comply with the final rule.

We have created a website, and you can follow that link and get to the information that we have found so far, and this is a very dynamic process for APHL, so we continue to get input from our members, and try to describe try to define better the questions that we will be seeking guidance from FDA.

And again, this is broad for all of public health activities, but also very precise on the newborn screening aspect of the public health laboratory work because that is an area where we believe the final rule could have a significant impact.

Our board of directors asked us to create a taskforce of APHL members who will be meeting on a

regular basis, and also getting information from our members, APHL laboratory members and federal partners, to best understand how the final rule can impact public health laboratory operations, and how we can share information with FDA.

So, the taskforce was approved. It has been formed. It has met a couple of times already, and we have a monthly schedule for them for the duration of our efforts to try to again, try to both understand the impact, and provide useful information to the FDA. And again, the materials and the understandings, the learnings that develop from the taskforce activities will cycle back into our website, our webpage on LDT resources, so that we can share it most broadly.

The next slide gets to some of the actions that we are also providing. Our board of directors, we have regular monthly meetings of our board of directors, and we include updates to them on how the taskforce is going, and the meetings and conversations that we are

having.

Again, we are in the process of developing templates for our member laboratories to use to come into compliance with the FDA final rule. Most of our laboratories really do not have this level of interaction with FDA, meaning they have not been in the process of even basically communicating much with FDA about laboratory developed tests, and so this is very, very new for just about all of them.

And we are looking to provide materials that are going to make it easier, not only for them to understand, but for them to submit the information that FDA is going to find useful. And, you heard mention of the challenge that our federal partners at FDA have, and directly commenting on the final rule because of the litigation, and for those who may not be aware, I'll just say that the litigation, the final documents that FDA will file in the court's challenge to its authority to even pursue a rule on lab developed tests, will be

filed by FDA at the beginning of December.

And there is I think some sense that after those final documents are filed the beginning of December, that it will take some time, perhaps to the middle of summer, next summer, 2025, before there is an initial court's decision.

And the reason I'm using the word "initial" here is because I believe that that initial court decision is likely to be mixed, meaning that it will find in favor of FDA in some instances, and in favor of those challenging FDA in other instances, and then that will likely lead to additional litigation, so I think that this is going to be something that the court will be spending time on courts, I should say, will be spending time on for well, for quite a while, is what I would say.

So, if I haven't emphasized it enough already, let me come back to the fact that newborn screening is, as I'm guessing you've heard already,

presents a unique challenge to the public health laboratories because so much of the work done for newborn screening is done using lab developed tests, and that is especially true when it comes to disorders that are added to the RUSP, and then implemented by the state programs.

I believe at APHL we have discovered that it takes on average two to three years after a disorder has been added to the RUSP, for a FDA cleared test to come into existence, and so that is a challenge that we are aware of, and would want obviously to be able to screen using a lab developed test until a commercially available test might be developed.

The next slide will have links to many of the things that you've heard me already talk about here, and if you just want a sort of a nice overview, I strongly recommend looking at the webinar that is listed on the second bullet there. There's also some FDA webinars that are all quite good on what the final rule looks

like. There are links to the court to challenges that have been filed in court by ACLA, and by the Association for Molecular Pathology.

And then there is a reference to the House Appropriations report language, and the reason that we're including that reference and link is that the House Appropriations report language specifies that FDA will not implement the final rule. And the language itself is significant because it is language directing from a, you know, body of the Congress, the House, directing FDA to not implement.

Some might observe that the language might have been stronger had it been bill language, and not report language, and that the bill language would have specifically prohibited FDA from spending any money implementing the final rule. This is different. This is not that, but it is directive from Congress, so and it is included in the agriculture appropriations bill, which is what funds FDA unlike all of the rest of the

Health and Human Services operating divisions.

There has not been a resolution to the agriculture appropriations bill, or any other appropriations bill, for those of you who follow federal funding, for the current fiscal year that we are in, federal fiscal year 2025, which began October 1st, so what that means is it is unclear whether the report language in the House bill is something that will ultimately wind up in the final agricultural appropriations bill report language.

The Senate has no similar language. The Senate is silent on that issue, so we'll when we get to making decisions about funding for the remainder of federal fiscal year '25, we will learn about whether that report the directive report language will stand in the final version.

And then on the next slide there we go, so this is a reminder. We have the email inbox, if you will, LDT questions @ APHL.org, and you can again see my

name and email address, and more importantly Mandi Cosser's name and email address, and I go back to the Chair to determine if we just flow right into Dr. Shone.

CHAIR CALONGE: Go ahead Scott.

DR. SHONE: Okie dokey. All right, well thanks, thank you to Ned for having me speak today. You know Peter gave a great overview of sort of the background and history of what APHL is doing to facilitate the public health labs and our response to this.

You know, a couple things before I go in. There is already a lot of talk of what's going to change, where are we going to go, you know, Peter highlighted the House report. You know, nobody knows. And so, the reality is that as particularly in my role as a public health laboratory director, I find it proven and responsible to prepare for what we know is on the books right now, and what is currently scheduled to impact our testing, and I'll focus on that.

I'm also going to try to keep this a little higher level, not get lab-geeky on everybody, so that there's a little more level of understanding of what we're talking about, but I'm happy to go into as much detail and excruciating level of science laboratory science during the Q and A if that's where you want to take me. So, the next slide please.

As Ned mentioned, I'm an Org rep from ASTHO, but I am not representing them at this time on this talk, and I am the lab director from the State of North Carolina, but HHS is not specifically behind sort of my interpretation of where we're going, though they are supporting me in doing this as a lab director, so next slide please.

So, real quick, I just wanted to highlight what are we talking about here, these are IVDs, or invitro diagnostic tests, so what's an IVD test? It's any test that's done on a sample, such as blood, in this case dry blood spots that have been taken from a human

body, and they're used to detect diseases, conditions, help monitor someone's health overall, basically any test that's used in the process of treating or making a medical diagnosis, that is an IVD.

And FDA regulates IVDs, and they have a risk-based classification system from low risk to high risk, and they are and these tests and these IVDs are evaluated based on that risk assessment. Many, many tests in newborn screening are cleared by the FDA as IVDs. I didn't say approved. FDA doesn't approve tests, they clear them for use in a certain category, and that's a critical distinction because we often hear the misappropriation of FDA approved.

A federal agency isn't going to approve a test, so they clear it for use. For example, our tandem mass spectrometry kits, digital microfluidics for lysosomal storage disorders, our immune assays for galactosemia and hypothyroidism, are all examples of FDA cleared tests that we use every day in newborn screening

laboratories.

Now, some people choose to use laboratory developed tests. Next slide please. And laboratory developed tests are defined as IVDs, these invitro diagnostics, that are intended to clinical use, so they are intended for use to diagnose or identify a condition in a human, right.

There's surveillance testing. You know, I get a bunch of deidentified flu samples submitted to my lab every year to look for novel flu emerging. Those don't have patient identifiers. We don't use them to treat and prescribe Tamiflu. Those are not covered by this laboratory developed test issue. We're talking about identifiable, for diagnostic purposes.

And some may say well, Scott, we're screening. We're not doing diagnosis. No, no, no, that's a screening test is still a diagnostic test because it leads to some type of medical outcome for a patient. In this case, the newborn. It goes to another

physician to have more testing done that does lead to a diagnosis, but there is an actual action on behalf of the human person for the outcome of this test.

So, it's intended for clinical use, and the LDT is typically designed manufactured and used within a single lab, so I have an LDT say for measles testing. The Maryland Department of Health lab might have a different LDT, but they've developed and validated in their lab for that specific purpose in their lab.

Now, LDTs include those tests I just highlighted, which are developed and run within a lab, but also the FDA cleared tests I just mentioned, if we modify them at all, they then become a laboratory developed test, and fall under this rule. So, the most commonly known one that I'll talk about later is cystic fibrosis variant, the 139 Illumina test.

It is FDA cleared for use in whole blood, but most newborn screening laboratories use it on dry blood spots. That has made that test an LDT, and we've had to

validate it for use within our lab as a laboratory developed test, okay? Next slide please.

So, why does anybody care about this? Well, forever FDA has used enforcement discretion. That is where an agency can bypass the regulatory requirements because risk is low, or the benefit to the public is high. In this case FDA has historically used enforcement discretion for LDTs. They've allowed clinical laboratory directors such as me to have my staff perform a validation.

I review it, I sign off on it, and we can use it, and I monitor for quality process in my lab. So, that has waived the requirements to register the test with the FDA, to report adverse events to the FDA, to label my test, to advertise it to make it publicly available as performance metrics, and also to subject it to good manufacturing practices.

All of that has been waived, which is typical for an IVD for LDTs, so that's what's changing. Next

slide. So, the FDA has announced that last year as Peter said, that they will begin a five year phase out, starting the clock started May of this year, May of '24 the five year phase out began.

And in that phase out policy the final rule says that LDTs will now be regulated by FDA as an IVD, and that those of us who develop and use LDTs will have to follow all of the practices I just said that has historically been under enforcement discretion for LDTs, and that's across the board.

We're going to talk more about newborn screening, but this is infectious disease testing. This is blood lead testing. This is all of those laboratory developed tests where there is no FDA cleared test on the market, or where labs have intentionally chosen an LDT because it might be faster. It might be more efficient.

It often is a heck of a lot cheaper, and so labs have often chosen LDTs for a number of reasons,

okay, not just because the test doesn't exist, which is a major issue in newborn screening for rare diseases, but also because an FDA cleared kit can cost $6,000.00 to run say 960 samples, whereas an LDT could cost maybe a $1,000.00, and that is a huge money savings, particularly for a cash strapped program like public health and public health newborn screening. Next slide please.

So, the five year phase out looks like this. And it is based on the risk categories, but everybody has something to do in May of next year, so six months from now, less than six months, five months and three weeks, that we all who have LDTs have to register them, and report them to FDA, okay.

We have to let FDA know we have these LDTs or we're running them. We also have to have in place a quality management system that can receive complaints, so if anybody is tested with one of our LDTs, and they want to file a complaint, we have to have a system in

place to receive that complaint, and then share that with FDA.

And then you can see on my slide, over each subsequent May there are more and more requirements as part of the phase out, until May of '28, LDTs that didn't exist before May of '24, have to either go away, and we have to switch to an FDA cleared method if it exists, or we have to submit it to FDA for pre market review.

FDA has already said that they anticipate that newborn screening tests will fall under moderate complexity moderate risk, sorry. Moderate risk, which is on the last slide. The high risks are going to be in November of '27. And so, that's the issue, right? So if you had an LDT running before May of this year, you don't have to submit it for pre market review, but you still have to submit to FDA that you're running it, and have a quality management system to monitor it.

And as Peter said, most of us, if not all of

us, are running LDTs in newborn screening, much less across our public health laboratories. Next slide please. So, I'm going to finish by talking about what is like the quick impact on newborn screening, but what am I doing in North Carolina with my team to prepare for this.

So, most labs are running their SCID and SMA testing on a laboratory developed test. It's quick, cheap and easy, and it is a highly, highly accurate and effective test. I mentioned Cystic Fibrosis variant detection, but also lots of us are running a GI test for galactosemia, and hemoglobinopathies, those are all laboratory developed tests.

And then many of us are running XALD tests that we have found to be more efficient than the FDA cleared test, okay. And so, these are all tests that if we're already running so be it, that's fine. We have to report them and monitor them, but it also means we can't change them because if they change, they have to be

revalidated, and now part of the new regulatory process.

And we've already talked about some of the new emerging tests. The new conditions that were just added to the RUSP, there's no FDA cleared tests for these yet, MPS 2, GAMT, we talked about MLD today with Alex's presentation, and all of the conversation around genomic sequencing.

There are only I don't know the number, but there are far fewer FDA cleared genomic sequencing panels than there are say what the vision for newborn screening is in terms of genomic sequencing. And so where this field is going is going to be impacted by this rule.

So, what am I doing in North Carolina? Well, the first thing is you know, we've began working on this a couple months ago. We've pulled our team together because as I said, I overview the whole lab, not just newborn screening, so I have to worry about newborn screening a lot, but I have all of my other tests that

are LDTs as well.

And so, we begin to assess the costs. You know, what is the cost of doing this business moving forward? How much staff do I need to monitor the regulatory components of this? What is the paperwork burden that's going to have to be submitted to FDA? We have biweekly meetings to talk about all of this planning for getting ready for just May 2025, right.

The problem, as Peter highlighted, is that there's more questions than answers. FDA has been doing a great job of getting guidance out, but there's still webinars planned in advance of May '25, that will give us guidance for how do we comply with the May '25 deadline.

So, there are some challenges there. In addition, the quality management system requires software, so we have data modernization challenges. We have to be able to accept those complaints and feedback from the public, so we have new communication method

needed.

And as I said, we probably need new staff just to shoulder the burden of this. And then moving forward it's a case-by-case decision. Do we want to pursue an LDT, or do we want to hold off until an FDA cleared test comes along? And this runs head on with RUSP alignment legislation.

North Carolina is a state that has a three year RUSP alignment rule, and so how does that balance out? Do I have to go to my legislature and say we don't have an FDA cleared test to bring an LDT on. It's going to take this long, and this much money, this many people? And how does that balance out with the populations we serve?

And so, those are all really huge challenges that we face right now in newborn screening and public health in general when it comes to this regulatory oversight. I will say finally that I'm a firm believer that quality management of LDTs is critical. I am not

against quality oversight of laboratory developed tests, okay.

We got here because there are some pretty awful LDTs out there that take advantage of some very sick individuals in our population. And so, there needs to be quality oversight of this. And the vision I shared from North Carolina is sort of what I take as a middle of road moderate approach. I have colleagues who are just going to ignore this, thinking it's either going to go away, or we'll deal with it in three to four years, when it actually becomes a major concern.

I have colleagues who have decided to stop LDTs altogether because they don't have the resources, bandwidth, or real expertise to deal with it. And I'm lucky enough here in my state that I have enough staff, and with regulatory experience, that we can navigate this together, and make sure that I am still balancing that load, that I am working towards bringing MPS 2 and GAMT online in a manner that I feel comfortable

submitting to FDA when that time comes.

But again, that isn't going to be the approach across the country, and so I think that we're going to have to recognize this, Dr. Calonge, as we move forward. That's my slides. I'm happy to answer any questions with Peter.

CHAIR CALONGE: Thanks Scott, and thanks Peter, very interesting and I learned a lot, Scott, about, you know, what our labs should be doing in screening for a number of conditions when the final rule is final, but it's been quite helpful.

Committee Discussion

CHAIR CALONGE: Let me open things up for questions, and I'm going to start with Jannine.

DR. CODY: First, my apologies. I had to step away, so I missed the very beginning of this conversation, but what is the problem this is trying to solve?

DR. SHONE: I will share my thoughts on why this change, right. So, right now any high complexity clinical laboratory, so you know, with a CLIA certificate can develop a test, and the lab director can say this is this has the appropriate metrics, and the appropriate characteristics to do what we say it does, okay?

And for someone like me with high quality standards, and for the public health lab directors across this country with high quality standards, I don't view that to be the issue. The issue is when you have rare conditions, rare cancers, rare disorders that rely on a one off say genetic test, or a one off or a biomarker that isn't necessarily widely accepted as an indicator, yet markets that and sells that there are concerns about that being available widely for, you know, laboratory medicine.

And so one could argue that this is a broad swipe approach at a more focused problem, however, the

reality is that FDA and Congress have tried to get a handle on the lack of oversight of laboratory developed tests for quite a while, and this has culminated in what we have now, which is the final rule.

There has been legislative efforts in the Senate historically that just didn't go anywhere, and then this is the second attempt at regulatory changes, and this one, you know, has gone through. And so, that's really I think underpinning that. Peter might have a different perspective from his policy role.

MR. KYRIACOPOULOS: Thanks Scott, so no, I think that's it, that there have been some pretty bad examples, and FDA is not able to act on them, and so now they're devising a way to stop those from happening in the future.

CHAIR CALONGE: Ash?

DR. LAL: So, I think the, the not being a laboratory person would say I think I'm just wondering if the problem with complying with the new rule would be

compounded by the fact that there are multiple and little methods for the same diagnosis, the same screening. And why, if that is the case, then why do multiple methods exist and can the APHL help to consolidate them so in a way that it's easier for maybe one or a few methods to just be approved rather than in every state have to do it on their own.

DR. SHONE: So, I just want to make sure I have the question correctly because I heard why do we have multiple different types of tests for the same, like to look for the same, okay.

DR. LAL: That is correct.

DR. SHONE: That exists across laboratory diagnostics, right. There are different tests to look for, you know, if I go I'm in North Carolina. If I go to the UNC lab to have say, you know, a Rubella test, and I go to the Duke lab to have a Rubella test, and I go to WakeMed to have a Rubella test, I'm going to have three different types of tests looking for the same

pathogen.

So, that exists across the laboratory, and so what historically has been with FDA cleared test, is the ideas that by having the regulatory oversight the federal agency has assured that the performance metrics of these tests are comparable, right? And so, that no matter where you go you should have the same condition, you have the same answer.

And that's the attempt here around laboratory developed tests is to achieve that quality oversight of assuring that if you get your results one way or another, you're going to have the same thing. I will also say that we've learned, and I think CF is a good example, and I see Michele has her hand up, so hopefully she agrees with this, it is that some states have decided necessarily to expand their panel for variant detection based on their population.

And so, sometimes they have they are running a different test, and I probably shot myself in

the foot by going to a genetic test, particularly one that's currently under discussion at national guidance level, but expanding the variant panel in a state like New York, versus other states that have at least right now decided not to expand beyond what's available from the Illumina 139 panel.

CHAIR CALONGE: Carla?

DR. CUTHBERT: Thank you both for this really very helpful discussion. Mine is not a question, as much as it is just a comment. Just to let you guys know what CDC has been doing to really help well, to try to parse out how we can help support our programs.

Peter mentioned taskforce that's been set up. We do have representatives from CDC on that particular group, and are looking forward to working with APHL, to identify resources and so on that can help newborn screening needs. So, several months ago when this was put out members of our branch did engage in a number of different conversations across CDC with their division,

with their colleagues at FDA.

We tried to understand what could be done. What we are working on right now is assessing different kinds of CDC wide and division wide support, to help with that integrated approach as well for compliance. We're looking, just as Peter had mentioned, evaluating sort of materials, templates and so on that currently exists within various centers within CDC to cover things like design and development of validation, and implementation process that are necessary for part of this FDA package to help with sort of a customized approach, so it certainly will be working with APHL with that.

Similarly with SOPs, and so on, from other parts of the agencies. One of the things that we've been thinking about for a while is that if it's needed, we're looking at leveraging or exploring compliant processes, or packaging reagents for dispensing, labeling and packaging and so on, to help provide

laboratory newborn screening laboratories with reagent handling that meet the quality system requirements.

And certainly, I think Ash was asking about this, about a more harmonized approach. Scott was correct, you go to a different laboratory, and you get a different method because that's just how it's done. But we are going to be having conversations with the APHL QAQC Subcommittee to investigate ways that we might be able to standardize multiplex biomarker evaluation.

Not a trivial task, but we are going to be having a heavier focus on that, and with respect to our reference materials at CDC we're certainly looking at trying to understand how we can leverage our materials to be able to help with that as well, so I'll just I'll put my hand down. That's just want I wanted to comment on.

CHAIR CALONGE: It's very helpful information, Carla, and thanks for chiming in, and

adding more to the very complex issue. Michele?

DR. CAGGANA: Hi. Michele Caggana from the Committee. I just wanted to thank both Peter and Scott for their talks this afternoon, and I agree 100%, there's been a lot of hand-wringing about this in the community. As a whole it's been talked about in many different committee settings with APHL and others.

And so, I'm wondering if there's some sort of a mechanism to formally from this Committee to let the Secretary of Health and Human Services know that this is a big concern of ours. It's a concern on service delivery with the newborn screening, but also as you heard from Scott, public health in general.

And I think the rule at its core, while you know, I feel like obviously everyone wants to do quality work. We want to have a quality management system in place, but the rule itself is sort of conflict to what the charge of this Committee is, and all the work that we do to add conditions to programs as quickly as

possible, and as soon as it goes through the entire evidence review.

And so, it's got to open the door. The CF example, so we have recommendations from the CF Foundation that were out for comment for newborn screening, where they are saying to get the most comprehensive CF genome, you know, CFTR gene sequencing test out there, and there's no FDA cleared assay for that.

In fact, the FDA cleared assays that are available now, just you know, run into the wall when you're thinking about doing equitable screening, and so we have sort of this charge to do screening as equitably as possible, and then we also have this, you know, the two things are going to collide with each other because of diverse populations in the, you know, across the country.

And it's particularly my state, so I'm just wondering if there is a way we could write a letter. Do

we have that power? Is there some mechanism outside of our usual charge of what we've been doing in the past.

CHAIR CALONGE: Well, I can't I don't think that there's anything in our charter, or in our enabling statute that says we can't write a letter. I think letting the Secretary, letting the FDA understand our concerns and the impact, even with the phase out rule, this rule will have on the practice of newborn screening in states across the country, I think is a very important thing to comment on, and to provide our input on, and so you know, Jeff, I think talking with Michael, and then the administrator, you know, we would like to write a letter expressing our concerns about this rule, something I'd like to pursue and see if we couldn't do that.

DR. BROSCO: I defer to Leticia as the DFO, but as I understand it this Committee has the ability to make recommendations to the HHS Secretary, so if there are concerns then it's appropriate to draft something,

and send it along for further consideration. Leticia?

COMMANDER MANNING: Yes, that's correct.

CHAIR CALONGE: Well, I wonder what process we should use, so maybe there's a smaller group of us that might be able to draft a letter. Leticia, do you think we have to vote on the letter, or you know we can't vote today, but we can get a general agreement I think from the Committee that this is something we might pursue.

But once we draft the letter does it have to be approved by the entire Committee in a formal meeting, or do you have other routes to get it moving a little quicker?

COMMANDER MANNING: Yeah. It does not have to be approved via vote, but we can send it out to all of the Committee Members for them to review, and get their feedback on, but it does not have to be any kind of formal vote.

CHAIR CALONGE: So, why not after this

meeting I'll start working on a draft that we can get out to the rest of the Committee and take input, try to see if we can get our concerns as an Advisory Committee on Heritable Disorders in Newborns and Children in front of the folks making the decisions around this issue. Ash?

DR. LAL: And I just wanted to get a little more agreed estimate of is this going to be disruptive to the current conditions being screened? I think there's been a lot of emphasis on introducing new tests for the conditions that are currently going to be nominated and come back in the next few years.

CHAIR CALONGE: Well, in our state we will have to stop screening for three RUSP conditions.

DR. LAL: But to get a wider picture of that

CHAIR CALONGE: Yeah. And I think it varies, if I'm correct, Peter and Scott kind of varies by laboratory.

DR. SHONE: So, you know, in terms of

existing conditions, Ash, is that if the laboratory doesn't have the resources to register their LDTs, and monitor them as I described, then the only alternative is to stop running them. And that's really that's at the heart that's really at the, I think most critical piece of what I think you asked, is that yes, it can stifle progress on the new conditions were an FDA cleared test doesn't exist, but there are tests we run now where there aren't. I mean there are a handful, right, as I said some labs have chosen to do an LDT because it is perhaps performs better, honestly.

That there are LDTs that do perform better than FDA cleared tests, and they're often as I said, a lot cheaper. And so, a lab will have to shift to an existing FDA cleared test of all the LDT that exists, or if it doesn't and they can't do what's required as part of the phase out policy, the only option is to stop running it.

And so, that could mean, you know, if I

couldn't do it in North Carolina, then that could mean I would have to stop doing GALT DNA testing. I will say, again, we started running this before May of this year, so any LDT that existed before May of this year is legacied from a pre-market review, but still has to be monitored, so there's still work.

Like it's not trivial, and so there is a potential impact on existing tests if a laboratory and we focus on public health labs because we're the first, you know, the first line of screening, but you know, and I'm not in a position to talk about the diagnostic labs. They typically have more resources, and could potentially do this, but we haven't I don't think we've heard from all of them.

And particularly those who are only running it for us are they going to maintain and monitor some of those second and third tier, higher tier testing that we're about to hear about actually.

CHAIR CALONGE: Michele? Oh, I'm sorry go

ahead, Ash.

DR. LAL: Ned, if that is indeed a real potential for disruption to current screening, then that is directly the Committee's business I think, once we have a little more of a handle on what the extent of the disruption is going to be, then I think the letter I would fully support on drafting a letter. Thank you.

CHAIR CALONGE: Michele?

DR. CAGGANA. Michele Caggana. I think one of the other things that Scott sort of mentioned, but maybe he didn't say crystal clear, it's not even the FDA cleared test. Some labs are going to get new equipment to do the tests, so it's not even the cost of going to the new assay. You may have to build equipment, get equipment, or find people that can run the new test, and there's a lot of things that go into this.

You don't just sort of buy it off the shelf and use it, especially because many of us have been doing these LDTs the same way for many years, it's much

easier for us to add something to an LDT platform, then a FDA, you can't alter them, so that's another concern.

CHAIR CALONGE: Cindy?

DR. POWELL: Yeah. I was asked to also remind everyone about the fact that many of the confirmatory tests done to confirm newborn screening conditions are LDTs, so this is also going to have a large impact on that, and probably put a halt to some of the requirements in order to, you know, confirm cases and/or not, so there's certainly concerns about that too.

CHAIR CALONGE: Thanks. Susan?

DR. TANKSLEY: Hi. Susan Tanksley, Association of Public Health Labs. And kind of to add to what Dr. Powell just mentioned, another concern in there is so public health labs, there's an exemption from the fee for public health labs, at least for the registration, or like the submission of them, but that's not true for reference labs.

And that fee is pretty extraordinary, so it does have potential, huge implications, for reference labs who are primarily doing these diagnostic tests.

CHAIR CALONGE: Debbie, are you holding up your hand?

DR. FREEDENBERG: I am. For some reason I don't have a raise hand, but I just wanted to, you know, kind of reiterate Cindy's concern, the referral the confirmatory laboratory testing, and the referral labs that are doing some of the confirmatory testing that's needed are very much doing laboratory developed tests, and that there, you know, for the genetics community as Cindy can attest to, is a lot more than just newborn screening that we're talking about.

I mean we're talking about almost all the testing that's being done on the genetics diagnostic side as well, and so I think that there is a very huge concern regarding the possibility of not being able to do this testing anymore, and you know, for a lot of the

conditions, luckily not necessarily newborn screening, there are only one or two labs in the country that are doing the testing at all, and so then that would, you know, even add more difficulty onto that.

So, anyway, I just wanted to add on my two cents to the clinical side of this.

CHAIR CALONGE: As I listen well, first ask this question, and then other people talk, should we ask it a little bit more broadly to document across a number of programs that impact? I don't believe I've listened to Peter, if necessary ask APHL to undertake that activity, but I do wonder if it's something that we should do to provide additional context to the breadth of the impact.

Because, as I said, different laboratory directors have spoken. It sounds like there would be variation in the impact for different programs. And it will impact it sounds like it will impact lower resourced programs more than perhaps those better

equipped programs.

MR. KYRIACOPOULOS: I was waiting for Peter to unmute, but APHL on behalf of the public health labs has collected with Mandi Cosser a lot of a lot, probably not everything you just asked for Ned, but that exists. It's on the APHL website that Peter highlighted, but I'm sure that can be further summarized.

And there are pages of specific examples from different public health labs on the differential health impact as you highlighted. There's probably more to get, but there's a huge start, and that was actually submitted by APHL on behalf of us member laboratories to FDA during the comment period.

CHAIR CALONGE: Okay. Thanks. I don't want to reinvent the wheel.

MR. KYRIACOPOULOS: I'd be happy to help you find those references.

CHAIR CALONGE: Appreciate it, Peter, thanks.

MR. KYRIACOPOULOS: Well the and option is the thing that FDA spent a lot of time looking at the state of New York clinical laboratory valuation program, and they liked that a lot, so we should all just send our newborn screening samples to New York, and they can then be exempt from the FDA requirement.

CHAIR CALONGE: Thanks. Well, I appreciate the presentations. They were excellent, and thanks for sharing with us today, and for your time today. And I keep having direction for the Committee that we'll get moving on when this meeting is done, and look for that in your email, and we'll probably put a little note in there saying please do this.

Please do this in a timely manner so we can get our comments and our position in front of the decision makers as early as possible.

MR. KYRIACOPOULOS: Thank you for having me.

CHAIR CALONGE: Thank you.

Higher-Tier Screening Ad Hoc Topic Group Update

CHAIR CALONGE: Well, we have one more presentation today. The HRSA NBS Excel program, as you know, is leading a couple of ad hoc topic groups for the ACHDNC. Back in August we received an uptake from the condition naming and secondary conditions workgroup, and today we'll be hearing from the Higher Tier Screening Ad Hoc Topic Group.

For that process I'd like to introduce Shawn Moloney, who is the manager for Michigan's Newborn Screening Laboratory since 2022. She oversees the activities of the newborn screening laboratory, including quality assurance, efficiency testing programs, and reporting presumptive positives to the follow-up section.

She is currently pursuing her DRPH in public health, and quick laboratory science and practice at the University of South Florida. Shawn Moloney served as the Chair for this ad hoc topic group, and we're really

thrilled to have you present to us today, welcome Shawn.

DR. MOLONEY: Thank you. That is not the right presentation.

CHAIR CALONGE: Yeah. It doesn't look like the right presentation.

DR. MOLONEY: No. I'm not talking about home queued sequencing though, fascinating topic, but not today. Thank you very much. Good afternoon, and I appreciate the opportunity to give this Committee an update on the Higher Tier Testing Workgroup activities. Next slide.

Today I will be presenting background on the Higher Tier Testing Workgroup, and an overview of the in person meeting, the 2024 higher tier testing survey results, the potential solutions, and resources to identify barriers, next steps, future activities and priority conditions.

Priority conditions are RUSP conditions, which the newborn screening programs thought higher tier

testing was most needed. Next slide please. The Higher Tier Workgroup is an ad hoc workgroup under the new steps, rare disorders subcommittee.

The workgroup was charged with proposing model practices to build a higher tier testing program model of collaboration to identity and discuss considerations to implementing higher tier testing in house, or through outsourcing, and if barriers to higher tier testing differed between new and legacy RUSP conditions.

Before we could begin work we agreed on the definition we would use for the term higher tier testing, which is laboratory tests performed subsequent to initial test results, using the same dried blood spot specimen, for the purpose of further identifying significant information that improves or enhances the interpretation of the first tier results.

These laboratory tests examined different analytes or employed different methodologies from the

first tier assay. Our next step was to develop a survey to send to state and territory newborn screening programs. Once we had the survey results we held an in person meeting to review them. Next slide please.

The workgroup met in person this past July. We reviewed the survey responses, discussed facilitators and barriers to higher tier testing, started work on determining mechanisms to implement higher tier testing for new and extinct conditions, and had presentations on various higher tier practices from state programs and partners. Next slide please.

We also discussed talking points regarding the importance of higher tier testing, reviewed conditions requiring higher tier testing, and different testing options available, reviewed program, reported survey responses about facilitators and barriers to higher tier testing.

We began discussions of potential solutions and resources for barriers, and we began prioritization

of conditions needing higher tier testing. Next slide please. Next, I'm going to talk about the 2024 higher tier testing survey, and responses. Next slide please.

Overall, we had 30 newborn screening programs respond out of the 53 programs the survey was sent to. For question number one we asked is your program interested in adding or expanding higher tier testing to your newborn screening algorithms.

80% said yes, 20% said no. Next slide please. We asked the programs to explain their yes or no responses. For those that said yes, they were interested in expanding tier testing, there were some common themes. For LSDs there was a lot of focus on MPS 1 and MPS 2.

Other responses were to reduce false positives, and improve positive predictive value, update or expand Cystic Fibrosis second tier screening methods, add second tier screening for X-ALD, bring higher tier testing in house, and higher tier testing is already a

routine practice.

For those programs that said no, concerns were raised about how higher tier tests were typically laboratory developed tests, and with the FDA's new rule, they were not certain of the benefit to bring them in house. They're not cost effective for low volume states, and no expansion was planned as all higher tier testing was performed by outside laboratories. Next slide please.

We did use skip logic in this survey, so those who answered yes to question one also answered question two, which was if your program is interested in adding higher tier testing, what are the three main barriers preventing or delaying its implementation? The top selections were limited staffing, lack of FDA kit availability, lack of expertise, and limited funding. Next slide please.

All programs were given the opportunity to respond to this question. Does your program conduct

higher tier testing in house, or outsource testing to another laboratory? In house only 10%, outsource only 38%, and both was 52%. Next slide please.

Question four was would your newborn screening program be willing to conduct higher tier testing for other newborn screening programs? Yes, temporarily was 50%. Yes, routinely 39%. No was 11%. We did ask for clarification on the no responses, and for those that answered, the reasons given were, "It would depend on the sample load, and currently not in a position to test for others." Next slide please.

The next few questions will focus on in house higher tier testing. Question five is what are the three main facilitators that helped your newborn screening program conduct higher tier testing in house?

The top selections were technical assistance from other newborn screening programs, experts, or training. Program administration and advisory committee support, additional staffing expertise, clinical

specialist requests, and support, and enhanced infrastructure. Next slide please.

Question six was what are the three main challenges that your program encountered in the last year conducting higher tier testing in house? The top selections were staffing limitations, limited staff expertise and funding limitations. Next slide please. Question seven, what are the strategies and solutions your newborn screening program used to overcome these challenges to in house higher tier testing?

Grant opportunities was mentioned a handful of times, facilities management exemptions, core lab concept for sequencing, technical assistance from other state experts, significant support from clinicians and advisory committees, stakeholders requesting legislation. They asked for samples such as for CF or X-ALD, staff to receive vendor training on new instruments to become subject matter experts, and hiring subject matter experts.

Next slide please. Question eight was are there any policies or regulations that prohibit your newborn screening program from outsourcing higher tier testing to another newborn screening program or private laboratory if tier testing cannot be implemented in house for certain conditions? 83% said no. 17% said yes. Two programs said yes, but only one specified a reason, stating contract negotiations are prohibitive on both sides.

Next slide please. Question number nine was what are the three main challenges that your program has encountered in the last year outsourcing higher tier testing to another newborn screening program or a private laboratory? Those top selections were contracts and agreements, turnaround time, and insufficient dried blood spots. Next slide please.

Question ten, what are your suggestions or recommendations for overcoming these challenges to outsourcing higher tier testing? Participants responses

were more national standardization and harmonization of screening panels, work with administration to show the benefit of second tier screening, establish a central state laboratory as MOUs with other state agencies are easier to establish in a contract with commercial entities.

Assistance regarding future LDTs, make quality improvements to reduce the turnaround time to help offset the additional time for second tier testing, have a single location set up contracts and pay for the testing, routinely applying for grant opportunities. Next slide please.

Question 11 is how have you identified any gaps that need to be addressed before your program implements higher tier testing for additional conditions? Some of the responses were recruitment and retention, infrastructure, time consuming procurement process, the FDA rule for LDTs, ensure leadership understands the value of second tier testing, subject

matter experts, laboratory information, management system limitations;

The interpretation of results/variants of uncertain significance, standardization of information, and knowing what higher tier testing is available. Next slide please.

Question 12 was what additional support or resale sources would be helpful in overcoming the gaps of challenges initiating higher tier testing, whether in house or outsourcing? Those top responses were FDA kit availability, technical assistance and training, quality assurance materials and specimens, development of standardize protocols and guidelines. Next slide please.

Question 13 was please let us know which conditions you feel are most important for your program to add higher tier testing for in the next five years. This is a list of over 20 disorders that the newborn screening programs mentioned in the survey. As a

workgroup to focus our initial efforts we needed to come up with a manageable list of conditions.

The workgroup decided the priority disorders, which are on the left side of the slide, and have an asterisk next to them. They are all RUSP conditions, which the newborn screening programs thought higher tier testing was most needed. Next slide please.

Now, I'm going to discuss the potential solutions, resources to identify barriers, and action items or next steps. Next slide please. The discussion of the in person meeting that has shifted to potential solutions to barriers which are hindering the implementation of higher tier testing.

Highlights of that discussion are assistance with contracting and procurement issues, a cost assessment study, and develop a cost model. One center of excellence is not enough. Training, normalized sending out while simultaneously building capacity in house, networking, and piloting to determine the best

approach. Next slide please.

The action items and next steps are produce a cost study, cost model for programs to use. Policy statement and talking points resources; prioritize diseases needing tier testing from those where tier testing is just nice to have. Provide guidance to programs to assess when tier testing is needed versus cut off changes, or addition of ratios is needed.

Develop resources for programs such as higher tier algorithms, a list of what higher tier testing is available, and higher tier testing resource tool kit. Next slide please. And here is a list of the higher tier workgroup members, and I would like to thank everyone who was given and continues to give their time and expertise to the higher tier testing workgroup, thank you.

CHAIR CALONGE: Shawn, thank you so much. That was just a great presentation. And I want to congratulate and thank the working group for doing such

great work. I think you've provided a very pithy and condensed version of what I know was a great deal of activity and wrangling of discussion, so thanks so much to everyone who participated.

Committee Discussion

CHAIR CALONGE: I'd like to open the floor for questions for Shawn, and any other members of the workgroup who might be in attendance. Cindy?

DR. POWELL: Hi. Cindy Powell, ACMG Org rep. I don't have a question, but a comment to just you know, thank Shawn and thank the group for tackling this. It's something that as a clinician that's really bothered me over the years, you know, as new conditions are brought on, and you know, if the public health lab is not doing all the testing it's put on to, you know, their standard clinical care.

And I've had experiences with patients who have been coming in, you know, to our clinic for

confirmatory testing, and they get to the door, they get to check in, and they're told well, we you know, we don't accept your insurance company. You know, if you want to have your child seen here you're going to have to pay like often hundreds of dollars out of pocket.

And you know, since we're the main center that they would be coming to for the testing, really puts them in a very difficult situation, so I would especially like everyone to think about the families, and you know, what we're doing to them in situations like this, so as much as the newborn screening labs are able to do, I think this is you know, a great situation for regionalization of at least, you know, this higher tier testing, so thank you.

DR. MOLONEY: Thank you.

CHAIR CALONGE: Thank you Cindy. Carla?

DR. CUTHBERT: So, we really appreciate this workgroup for putting this together, and really parsing through the details of this. And again, we want to just

acknowledge that CDC has been actively involved in creating methods and second-tier tests, working towards expanding our quality assurance programs to ensure that these biomarkers are not just we don't just have tests for them.

That are multiplex, but we also are creating reference materials for both PT and quality control, as well as linearity methods, and these are active areas of expansion within our program to help support the newborn screening needs as identified. And most of the conditions that have been identified are ones that we have been have ranked as high priority programs for providing materials for.

They also include, again, the expansion for the CF variants, which we are working to create materials for as well. And we acknowledge that one center of excellence is not enough. I just want to respond to that. We get that, but we are certainly hoping to be able to have additional programs.

And just to let those who don't know that we do have workshops and technical assistance opportunities where states can call us up and ask for some of our Ph.D. level scientists to come and help implement conditions, and implement methods within their programs. It would be more ideal for them to have these positions themselves, but certainly the states can request these activities as needed.

So, I just want to let you know that we are looking at these as well, as we are very, very interested in also being supportive of these efforts as we move forward for being able to address these issues.

CHAIR CALONGE: Amy?

DR. GAVIGLIO: Yes, thank you. Amy Gaviglio, Org rep, NSGC, and I want to build a bit off of what Dr. Powell mentioned in that I think it is helpful for the Committee to recognize the benefit of tier testing, not just in laboratory performance, but truly in family experience, and not just kind of focusing on the

quantity of the diseases we screen for, but for the quality of that screening as well.

And so, I guess my question also kind of as a member of this workgroup is how to take it to the next level, and whether it is within the purview of the Committee to make recommendations for programs to employ this level of testing for certain diseases. It seems like there may be some precedent for this, both in terms of, you know, recommending succinylacetone for Tyrosinemia Type 1, Psychosine for Krabbe, but I'm wondering if that's something that the Committee would be willing to look at as it seems like a recommendation from the Committee might help in overcoming some of the barriers that programs have discussed in terms of justification of adding this type of testing to their algorithm.

CHAIR CALONGE: Thanks, Amy. You kind of were moving in the direction I was moving a little bit differently though, it's like this is great work,

and I think provided to the state laboratories could be quite useful. But then the question I was going to ask was what could the Committee do that would help with this process, or move things along.

And if we were to make recommendations around the issues who would we be recommending to? And that's something that Jeff and Leticia and other HRSA staff and I probably need to talk a little bit about, but I think you'd like to capitalize on this information and move it forward in a way that will be useful for the laboratories, and for diagnostics screening and diagnostic testing.

DR. BROSCO: Ned, if I could add to that because there are multiple ways that HRSA supports state labs, and I guess I'd like to hear a little bit more, particularly from the lab directors, from Christine and Michele, and Scott and so on, about what would be useful.

Because on one hand we don't think that we

want the federal government, or maybe this Committee and its advice, either HRSA or the Committee, we say oh you should do this, you should do that, you should do everything else because that's really their expertise.

And just to clarify, I think Krabbe where it was a higher tier, that was to clearly distinguish what condition was meeting criteria. It wasn't so much we think you should, you know, practice your lab stuff this way, so I'd love to hear from the lab directors what they would find most useful, either from HRSA or from the Advisory Committee.

CHAIR CALONGE: Christine?

DR. DORLEY: Yes. I think from the standpoint of being here in the newborn screening laboratory, many times to move ahead with something as far as a second tier assay, you need that little boost or support from laboratory administration to move ahead with adding the second tier test because it does cost money, and the purse strings are held by a higher

authority than that person in the laboratory.

And often times, and I'm not calling anyone out, definitely not the case in Maryland, but sometimes you don't have the support of your laboratory administration to move forward with the second tier, or higher tier assay for the very reason how newborn screening is defined as a screening assay.

And when you get into second tier or higher tier testing, some of it can be basically diagnostic, when you think about SMN 2 copy numbers. Some of the DNA assays that are used with the CFTR. You have two Delta F508 mutations on your CFTR 39 or 60 mutation panels, it's almost diagnostic.

And so, there can be some I guess help from putting out a statement, or something of that nature that says you know, second tier assays can improve positive predictive values. It can help with the specificity of assays because it's a big problem.

We're flooding the follow-up world with false

positives, and the sheer amount of dollars that go into following up a kid, just to eliminate that they don't have a disease could have been nipped in the bud from the very beginning. So, yeah, that's my two cents.

CHAIR CALONGE: Well, I appreciate that, Christine. I also think for the families it's a better solution than saying there may be a problem. In order to figure that out we have to refer you to a specialist for further testing, so I think, you know, if those are answers that can be addressed at the laboratory level before the parents are ever called, there's huge value I think, and harm reduction in that. I appreciate your comment. Michele?

DR. CAGGANA: I agree with Christine. I mean, I'll go old school, having something in your hand, a piece of paper that allows you to go to someone and say this is what the professional recommendation is, is helpful. It doesn't necessarily solve it a lot of the times, but it's still, I think, helpful, and certainly

can't hurt.

Another thing that people pay attention to is overall cost, right? So in New York we were referring a lot of babies with one variant in the CFTR gene because we knew we weren't detecting them because of the diversity of the population, and the panels were geared towards Caucasian white families that had CF, because that's where the body of knowledge was when those tests were developed.

And so, we used the rationalization that we would save costs downstream and parent anxiety by going next gen, because that's more expensive certainly, but we were able to sort of balance that out in the costs. And I'll just remind us that we're in the process of looking at MLD, and the recommendation is multi-tier testing, and so I think this is going to become more norm.

And we know there's a lot of work going on in Homocystinuria, and some of these other conditions right

now to make our tests better by doing second tier testing, or different analytes. And so, I think it's an evolving landscape, but it's certainly something that can't hurt to have something official from this Committee. Thank you.

CHAIR CALONGE: Thanks. Susan?

DR. TANKSLEY: Hi. Susan Tanksley, Association Public Health Laboratories. In my state in Texas, we've always tried to take the approach of what is, you know, what is the additional testing that can be done to put out better results, fewer false positives? What's going to be the least impact? But it has always been a challenge to calculate system costs, right?

So, we talk about newborn screening as a system, but it's literally impossible to calculate all the costs, and all the cost saving that are downstream, and those costs are to our laboratory. They are not there's a whole system cost, but our costs are to the lab, and the cost savings are downstream.

And so, that's a hard part on the budget of the labs, so we can save money downstream if we put the money upfront. And so that's where perhaps grants could assist in development of the second-tier tests, but I do you know, this ties into our last presentation on LDTs as well because I don't know if we have a second tier test that is not a lab developed test.

And as we add more conditions our intent is to add second tier and third tier tests, all of which will be lab developed tests, all of which will be subject to those regulations. And so, there is that direct tie in as well, thank you.

CHAIR CALONGE: Yeah. I knew someone was going to point that out. Susan, thanks. Well, this is great input, and Jeff, I think maybe we should circle back both at HRSA and then with our colleagues at CDC, and talk about you know, what kind of product statement or recommendation, and to whom it falls within the purview of this Committee and those agencies.

And Carla, I'm pulling in CDC because I know you're involved directly in this activity as well. And I think if there were a way to do a joint, or a position or recommendation, it could be very powerful coming from two agencies.

DR. CUTHBERT: Sounds good.

CHAIR CALONGE: Any other comment on this particular issue? That's great.

New Business

CHAIR CALONGE: I think we're a bit over time, but I want to move in and to allow a little bit of time for new business. I have notes that we have new business subjects from Melissa Parisi and Carla Cuthbert, and Melissa are you with us? And you want to talk a little bit about the NBS genome project?

DR. PARISI: Certainly. Thank you for an opportunity to present kind of a brand new initiative to this group, and to let you all know about one of the

projects that NIH has just started embarking upon that I didn't actually include in my summary of currently ongoing research programs. Hang on just a second.

So, this is a newborn screening by whole genome sequencing effort. It's being led by the NCATS Institute, which I talked to you a little bit earlier about, NICHD and NHGRI are also providing input into this new initiative. Next slide.

This is something that's under the auspices of what we call the common fund, and these are initiatives that involve multiple institutes across NIH. They try to really garner opportunities that may exist, and do rather bold things with modest amounts of funding.

And this is a new venture initiative, which was just launched in 2024, and is funding a couple of other projects as well, so this is the third one selected under this new mechanism of venture funding. So the goal here is to demonstrate that newborn

sequencing could be added into the newborn screening paradigm, and by basically testing the feasibility of adding whole genome sequencing into some state screening programs. The goal is to invest $5,000,000 per year for the next three years.

This is and I really want to emphasize this is a consented research study. We are not proposing that all states drop everything and start sequencing. And the goal here is really to provide more equitable access to whole genome sequencing, and keep pace with some of the therapeutic opportunities for treating rare diseases that are being developed, and are continuing to come down the pike. Next slide.

So, this is really a collaborative effort, and it's a model whereby we would like to roll out a newborn sequencing program across five to ten states with different capacities for actually adding sequencing into their workflows. We anticipate that this would include a centralized laboratory for analysis and

interpretation of genomic sequencing results.

We would focus only on a limited panel of genes that are associated with serious or life threatening rare diseases that have early treatment options available. So we are not proposing sequencing and giving back reams of data, including variants of uncertain significance. It would be a very carefully curated set of genes that are actionable.

We would hope that this could achieve equitable access to genomic sequencing in the newborn period by trying to do it on at least somewhat of a limited population basis, and very importantly, as I mentioned earlier today, we really want to include the ethical, legal and social implications of this type of research program in a state newborn screening system. Next slide.

And to that end, especially with regard to the ELSI component, we anticipate that this will establish a community advisory board, or boards, where

we would really take input from a wide variety of stakeholders, including parents, including newborn screening programs, including clinicians, many other perspectives about that have relevance for this particular program, and that will have opinions about how this is impacting them, and whether this is a good thing to do, or this is not a good thing to do.

So, we anticipate that this input would include ways in which we can engage the community, a strategy for informed consent, approaches to data sharing issues, which are not insignificant. Design of the research project, as we talked about earlier today, and how we could actually return results in a fair and equitable and valuable way for families and for providers.

We hope that this might bring new expertise t the newborn screening field, and we also will try do anticipate and engage diverse perspectives, including those that are screened, and those that are involved in

the research project. And I think I have one more slide that is a bit of an overview.

So, this has not been launched yet. I mean we basically got approval for this initiative in September, so this is really in its early infancy, but this is the potential structure for the program, and how we might envision that work. And you see on the left we have a community advisory board that would be giving input into the administrative functions in which that would include the oversight of the program, consenting, development of a disease and gene list, data storage issues, et cetera.

The community advisory board would also be giving input into activities related to participant recruitment and consent, as well as confirmatory testing and return of results, and that blue box there would interface with families with newborns, with providers in the neonatal period.

Off to the lower right, we would envision

that state public health laboratories, after consent was obtained, would be sending those blood spot punches for sequencing analysis, and then we would complete the cycle with again, confirming results, and returning results.

So, this is a very high level view. We're hoping to launch this within the next year in terms of at least putting the solicitation out by the end of this calendar year, and making an award by spring or summer of 2025, and then probably a year's worth of preparatory work prior to actually launching the sequencing per se.

So, that's what we're looking at. We've got three years to do it, and we really welcome feedback from the community. We were really grateful that at the APHL Newborn Screening Symposium, we had an opportunity to present this at a town hall meeting.

Dr. Dominique Pichard from the Office of Rare Diseases Research at NCATS and myself, and we got a lot of really valuable feedback, both positive and negative,

and ambivalent, and we look forward to hearing more from the community about this initiative as we move forward, so thank you for the time to present that.

CHAIR CALONGE: Thanks, and hopefully you'll make the slides be available, and individual panel members, the Organizational reps could have the opportunity to send you a comment and notes, and their opinions based upon your presentation.

DR. PARISI: Absolutely. Thank you.

CHAIR CALONGE: Carla, you have a CDC update on the CONPLAN?

DR. CUTHBERT: Sure. So the CDC, together with APHL and HRSA and with input from state departments of health, we recently revised the National Contingency Plan, or the CONPLAN for newborn screening, and this plan is designed to help states and regions, and groups of states to maintain important newborn screening operations during public health emergencies.

And version three of the CONPLAN is the

second update of the plan, and it provides more details about the different partners that are involved in the newborn screening systems, and their responsibilities. It also explains how emergency management assistance compact, or the EMAC system could be helpful, and it includes extra information to guide state program on to what to do before and after a newborn screening emergency occurs.

So, the CONPLAN has been signed by both CDC and HRSA, by Dr. Ari Bernstein at the CDC, and Dr. Michael Warren for HRSA, and CDC has already begun to work to finalize the formatting of the document, so that it could be accessed online. We plan to work with APHL to present a webinar early in 2025, to help states learn how to effectively use the CONPLAN in their own preparedness, and for response activities, and we look forward again to having this document be out and available for the newborn screening community. Thank you.

CHAIR CALONGE: Thanks, Carla. And I just want to add a final comment that Jannine Cody had asked a question about, talking about recommendations from the Committee that could impact screening and care at points other than newborn screening.

And this is a topic we talked about things like frequently, and what I wanted to tell Jannine was that something we should eventually think about we can craft some additional time at the February meeting to talk about planning about recommendations to impact care at places other than the newborn nursery.

So, I appreciate your interest, Jannine, it's a real interest of mine, and Jeff and I talked about it a fair amount of time as well, so it's time to think about should we move forward a little bit more formally about the same kind of ad hoc topic workgroup approach, or other strategies to kind of explore it a little bit further.

So, I wanted to make sure you knew I heard

you, or we heard you.

DR. CODY: Okay.

CHAIR CALONGE: And we'll, in the interest of ending let's put it off to February if that's okay.

DR. CODY: Yes. Thank you. I didn't know if it was just a topic I didn't know anything about, or if it was a general topic that needed that could be clarified for the entire Committee.

CHAIR CALONGE: Oh, I think it is, and Jannine posed a group of questions, all of which have answers, not all of which have satisfactory answers, but I think it's a great topic, and again, one that it gets back to that issue what else is the Committee charged with? We're heritable disorders of newborns and children.

DR. CODY: Children.

CHAIR CALONGE: And trying to make sure that we adopt full range of the possible intervention and screening points is relevant, so I appreciate that.

Let's see. Anything else for the good of the order today? We've read through our agenda. Remember that February 13th and 14th are our next meeting, which is the 20th anniversary. I suppose you could still make Valentine's Day plans if you need to, but we'll be spending at least part of that day together, and I look forward to seeing you all in Rockville next year.

Now, that being said, we will continue to work. We have a number of agenda items, and things we've identified today that we need to work on between now and the next meeting. You've heard that there are two, and potentially more preliminary nominations that are being considered that we're working with.

There's the ERG report on MLD, and then as I said, we continue to talk with the nominators regarding DMD. So, even though it seems like there's a few months, they will be busy months, and so I hope everyone has a great holiday season, and if we don't talk to you before, we'll be sure to be talking to you in 2025.

Leticia, am I forgetting anything before we adjourn?

COMMANDER MANNING: You covered everything. Thank you.

CHAIR CALONGE: All right. We'll see you all soon.

(Whereupon the Advisory Committee on Heritable Disorders in Newborns and Children adjourned at 4:00 p.m.)