THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS

5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Monday, January 29, 2024

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P R O C E E D I N G S

Welcome, Roll Call, Opening Remarks, and Committee Business

DR. CALONGE: Good morning. Welcome to the first Advisory Committee on Heritable Disorder in Newborns and Children meeting in 2024. And it's great to have so many people in the room. There are some people, including the Committee members I've not met in-person and it's great to flesh you out in all three dimensions.

I'm going to do a quick land acknowledgment, as we're gathered here in person at 5600 Fisher Lane, Rockville, Maryland, I want to open the meeting by taking a moment to acknowledge the land we gather on today. We acknowledge that the land and water on which our meeting is taking place was and still is inhabited and cared for by the Susquehannock Tribe, the Piscataway Peoples, including the Piscataway Conoy Tribe and the Choptico Band of the Piscataway Indian Nation.

We're grateful for their past and continued stewardship of this land and pay our respects to Maryland's indigenous community and their Elders, both past and present, as well as future generations.

Now, I'd like to turn things over to Leticia Manning for the roll call.

CDR. MANNING: Thank you. Good morning, everyone, and welcome to HRSA. I'm going to start with our Committee Members for roll call. From the Agency for Healthcare Research and Quality, Kamila Mistry.

DR. MISTRY: Here.

CDR. MANNING: Michele Caggana.

DR. CAGGANA: Here.

CDR. MANNING: We have Ned Calonge.

DR. CALONGE: Here.

CDR. MANNING: From the Centers for Disease Control and Prevention, Carla Cuthbert.

DR. CUTHBERT: I'm here.

CDR. MANNING: Jannine Cody.

DR. CODY: I'm present.

CDR. MANNING: Christine Dorley.

DR. DORLEY: Here.

CDR. MANNING: From the Food and Drug Administration, Paula Caposino.

DR. CAPOSINO: Here.

CDR. MANNING: From the Health Resources and Services Administration, Jeff Brosco.

DR. BROSCO: I'm here. Dr. Warren is at a

Maternal Health meeting today, but he should join us by the afternoon and will be here tomorrow for most of the agenda.

CDR. MANNING: Jennifer Kwon.

DR. KWON: Here.

CDR. MANNING: Ash Lal.

DR. LAL: Here.

CDR. MANNING: Shawn McCandless.

DR. MCCANDLESS: Here.

CDR. MANNING: From the National Institute of Health, Melissa Parisi.

DR. PARISI: Here.

CDR. MANNING: And Chanika Phornphutkul.

DR. PHORONPHUTKUL: Here.

CDR. MANNING: And for our organizational representatives, from the American Academy of Family Physicians, Robert Ostrander.

DR. OSTRANDER: Here.

CDR. MANNING: From the American Academy of Pediatrics, Debra Freedenberg.

DR. FREEDENBERG: Here.

CDR. MANNING: From the American College of Medical Genetics, Cindy Powell.

DR. POWELL: Here.

CDR. MANNING: From the American College of Obstetricians and Gynecologists, Steven Ralston.

(No response)

CDR. MANNING: From the Association of Maternal and Child Health?

(No response)

CDR. MANNING: From the Association of Public Health Laboratories, Susan Tanksley.

DR. TANKSLEY: Here.

CDR. MANNING: From the Association of State and Territorial Health Officials, Scott Shone.

DR. SHONE: Here.

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

(No response)

CDR. MANNING: From the Child Neurology Society, Margie Ream.

DR. REAM: Here.

CDR. MANNING: From the Department of Defense, Jacob Hogue.

(No response)

CDR. MANNING: From the Genetic Alliance, Natasha Bonhomme.

Ms. BONHOMME: Here.

CDR. MANNING: From the March of Dimes, Siobhan Dolan.

DR. DOLAN: Here.

CDR. MANNING: From the National Society of Genetic Counselors, Cate Walsh Vockley.

MS. WALSH VOCKLEY: Here.

CDR. MANNING: And from the Society for Inherited Metabolic Disorders, Sue Berry.

DR. BERRY: Here.

CDR. MANNING: Thank you, and that concludes our roll call. And now, I just have a couple of reminders for folks. In regards to conflict of interests, just as a reminder, this is an Advisory Committee to the Secretary of Health and Human Services. You should consider recusing yourself in all matters likely to affect the financial interest of any organization with which you serve as an officer, a director, a trustee, or general partner, unless you are also an employee of the organization, or unless you have received a waiver from HHS authorizing participation.

All Committee meetings are open to the public. Meetings and agenda topics are announced in the Federal Register so that the public has the opportunity

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

For the January meeting, in the Federal Register notice, we noted that there will be two public comment periods, one today and one tomorrow. Only with advance approval of the Chair or DFO may public participants question Committee Members or other presenters. Public participants may submit written statements. Also, public participants should be advised that Committee Members are given copies of all written statements submitted by the public.

As a reminder, it is stated in the Federal Register notice, as well as the registration website, that all written public comments are part of the official meeting record and are shared with Committee Members. Any further public participation will be solely at the discretion of the Chair and the designated federal officer or the DFO.

So, just a reminder for folks, for visitors here in the building, you should remain here on the fifth floor. You're not permitted to go upstairs. There is a cafe with some bites across the way here.

There's also a little store with smaller bites to the left there.

For bathrooms, there are four bathrooms here easily accessible on this floor. There is one to the right and to the left near the cafe, and there's also one to the right and the left just behind you here.

For those of you who are joining via webinar, the audio will come through our speakers. There's also a call-in option if for some reason your audio on your computer speaker isn't- working. Committee Members and organizational representatives, you should've received a special panelist link to log in. Please speak clearly and remember to state your name in order to ensure proper recording for the Committee transcripts and minutes.

And this note applies for those folks that are in person as well. Committee Members and organizational representatives, and for the folks that are providing your public comment, please speak clearly into the mike and state your name and your organization.

If you're having technical difficulties, please try reopening the webinar or using a different browser, or in your registration link there is an email address you can contact for assistance.

And I have one last note, the future meeting dates for the rest of 2024 there will be meetings that will be either in-person or hybrid May 9th through the 10th, August 8th through the 9th, and November 14th through the 15th. You can refer back to the ACHDNC website for more detailed information about the upcoming meetings and whether they'll be in person or hybrid. And now I'll turn it back over to Ned.

DR. CALONGE: Thanks, Leticia. As you're aware, the Committee spent a significant amount of time at the last meeting, and last year, assessing our processes. At the November meeting, we hosted four listening sessions to gather diverse stakeholder input about our nomination and review process, received a lot of great, thoughtful feedback, and I want to thank everyone who participated.

The common theme heard across the listening sessions was that our process of nominating a condition for the RUSP is difficult and burdensome and it doesn't consider some factors that we know are important to families. After thoughtful deliberation, the Committee decided there was a need to update the Committee's evidence nomination and review processes.

We decided on the basis of that, on a short

delay on accepting new conditions until May of 2024 in order to solicit additional feedback from stakeholders and to giving ad hoc topic groups consisting of stakeholder and Committee Members to look at our processes. I appreciate all those who participated in these meetings and the input they provided.

This afternoon I'll update the Committee and everyone here on the outcomes of these meetings. As a reminder, during this time HRSA staff and the Committee Chair, myself, remain available to provide technical assistance to potential nominators on core elements that are needed for nominations, such as the need for published data on the newborn screening tests, confirmation tests, short and long-term follow-up, treatment, and utility of identification pre-symptomatically versus through clinical ascertainment.

The previously nominated conditions that are in the evidence review process, which include Krabbe and Duchenne Muscular Dystrophy will follow the current process.

As many of you are aware, the National Academies of Sciences, Engineering, and Medicine is conducting a study examining the current landscape of

newborn screening systems and processes. Their search will also consider sustainable adoption of screening for new conditions using new technologies. The NASEM Committee will make recommendations for future improvements that help modernize newborn screening to be adaptable, flexible, coordinated, communicative, and capable of efficient and sustainable adoption of screening for new conditions with new technologies, as well as an equitable public health program from which all infants will benefit.

The next slide is based on a presentation by Alyssa Bank from the Office of Women's Health on Friday, January 26th. NASME's work will focus on the following. Examine the RUSP review and recommendation processes in light of existing and emerging technologies and consider how the Committee's evidenced-based review process currently works and if additional factors are needed to better understand harms and benefits and to anticipate- potential increase of nominated condition.

Next, examining state and federal capacities to strengthen screening processes and implementation of screening for new conditions added to the RUSP. Next, review existing and emerging technologies that would permit screening for new categories of conditions, then

research technological and infrastructure needs to improve diagnosis, follow-up, and public health surveillance. And finally, review NBS data collection processes for tracking disease prevalence, improving health outcomes, conducting longitudinal follow-up, ensuring health equity, defining the natural history of conditions that can be screened for, and measuring quality of life.

NASEM selected volunteers to serve as Committee Members for the study. They received over 250 nominees with diverse expertise as patients and family with lived experiences, state based NBS public health programs, clinic care, existing and emerging technologies, legal and bioethical implementations of newborn screening, and health care service delivery and payment, just to name a few of the areas of expertise.

We plan to have a robust engagement with the public to gain diverse perspectives, hosting virtual focus groups, public comment sessions at virtual information-gathering meetings, and opportunities for written comment. The first meeting of this Committee was this past Friday, January 26th. You can sign up for email updates and get details on further engagement plans. You can also submit written statements to the

Committee via the study's website and via email at newbornscreening@NAS.edu.

I would also like to update everyone on HRSA's Co-Propel Grants. So, the grant notice of funding opportunity or NOFO is open. The NBS Co-Propel Program builds on previously funded HRSA grants to strengthen collaborations between state, territorial, and public health agencies and with NBS partners, such as universities, nonprofits, or other institutions with expertise in newborn screening in order to achieve a common goal to improve access to services and outcomes for children identified with the heritable condition identified through NBS, so they are healthy, growing, and thriving.

The grant opportunity will close on February 23rd of this year and there's a technical assistance webinar scheduled for Wednesday, January 31, 2024, from 2:30 to 3:30 p.m., Eastern Time.

I want to thank Committee Members for reviewing the November minutes. We've had some Committee Members provide comments on the minutes and we're going to revise those after this meeting is over based on their input and then share updated versions with the Committee that we can review and adopt

tomorrow.

I'd like to talk a little bit about our topics for today. We're going to have presentations focusing on families and then after lunch we'll have public comments. After that will be an update from the ERG on Duchenne Muscular Dystrophy evidence-based review, then I'll provide a proposal for the public health assessment for the decision matrix and end the day with a discussion about our nomination and evidence-based review processes. So, it'll be a heavy presentation day and hopefully a great discussion day as well.

Then to preview tomorrow, the main focus will be on Krabbe disease, starting the morning with public comments, then a presentation from the ERG on the expedited evidence review for Krabbe, a Committee report from the Committee liaisons on Krabbe, and then a vote on adding Krabbe disease to the RUSP. We'll end the day with updates from APHL, the next steps program.

Family Outcomes of Newborn Screening: Project Overview Update

So, with that, I would like to launch into

the agenda for today. And sorry if I went fast, but I'm right on time, which is good. And I'm excited to welcome our first speaker, Dr. Don Bailey for RTI. He's going to talk about his work on family outcomes in newborn screening. You'll remember that last year we discussed family outcomes, and it continues to be a topic of great interest for the Committee.

As a result, HRSA funded APHL, who's working with RTI to assess domains of family outcomes in considering what should be measured for quality for life for individuals and families identified with heritable conditions through newborn screening. Dr. Bailey is a distinguished Fellow, RTI International, where he's a member of RTI's Genomics Translation Research Center. From 2011 through 2017, he served as a voting member on the Advisory Committee on Heritable Disorders in Newborns and Children.

Currently, his work focuses on the future of newborn screening, having published several recent papers on how newborn screening can prepare for a future of new, transformative treatments in genome sequencing. He's a senior science advisor for Early Check, a statewide research project to help prepare newborn screening for new conditions and new technology with a

current focus on whole genome sequencing.

And so, I see you made your way up to the podium, looking forward to your presentation.

DR. BAILEY: Thank you, Dr. Calonge, and thank you so much for having us here again today. I think I speak on behalf of Aaron and Sara and really so many families with children who've been impacted by newborn screening. We hope to be, and we appreciate having a morning devoted to families. This is really a great opportunity for us, and we thank you. Thank you for that opportunity.

So, I'll be describing the beginnings of a project called Family Outcomes in Newborn Screening, project background, and overview. This is funded through HRSA, by HRSA through a cooperative agreement with APHL. So, I'm speaking on behalf of our team today, so Elizabeth Reynolds and Melissa Raspa are here in the audience today. You may remember that Elizabeth joined me when we spoke last time we were here about our early intervention and newborn screeding work.

So, just to tell you a little bit about what I'm going to tell you, first, some summary points. Although newborn screening focuses mostly on benefits to the child, families certainly benefit as well. I think

we all know that. Really, very little work has been done to assess family outcomes of newborn screening and there's really no agreement on what those outcomes will be.

We can talk about quality of life. We can talk about confidence in child rearing. We can talk about knowledge of your child's condition, but there's not really been common agreement on what are the desired outcomes for families. We know what those outcomes are for children, for the most part. So, our team has a good bit of prior experience in developing an assessment tool to document family outcomes of Early Intervention and so we are building on those experiences to develop a tool and process to assess family outcomes in newborn screening.

Of course, we believe that such an instrument could be one important component to assess long-term outcomes in newborn screening in terms of benefits for families. Most of the focus today is going to be how we got to this point because we're just engaged in the very beginnings of this process, but I think you'll see from how we got here with our previous work. We'll be following much of the same protocol and processes that we did then.

Let me just begin with a couple of definitions. So, I start with the family-centered approach. Now, we can think back on 40 years ago - the Maternal and Child Health Bureau, Merle McPherson and a number of people back then were really focused on should services be family centered because the essential assumption is that young children cannot be viewed apart from their families, nor can services be provided without a consideration of the family context, so families really aren't clients receiving services, but are partners in making decisions about goals and activities. And you can see I've listed the core principles. These are actually pulled from an article that Merrill and others wrote many, many years ago.

Those core principles are really focusing on family strengths and diversity and decision-making and empowerment. So, we hope that newborn screening is also a family centered and I think that's an interesting question for us to be asking and maybe some days we can focus on that.

So, then a couple of other definitions related more specifically to our project, and I'm going to differentiate family satisfaction versus family outcomes. So, satisfaction is to the extent to which

families are satisfied or happy with various aspects of the program. Like I'm happy with the amount of services I received, or I think it's of high quality or this person was really great in supporting me, so it's an evaluation of the process.

An outcome is a benefit that families receive as a result of services. It's not with the receipt of services, but it's what happens as a result of those services. So, just an example of differentiation, so satisfaction might be how a family feels about the quality of the information provided about their child's health condition and the outcome is how well they actually understand the information, the nature and consequences of their child's health condition.

So, why would we be interested in assessing family outcomes? Well, the name of this Committee has heritable disorder in its name. Heritable disorders are, by definition, family disorders, not that the family is disordered, but you know what I'm saying. Child well-being really can't be fully understood without considering family context, so it's really a across the childhood age, but especially for infancy.

Of course, families pay critical roles in

their child's health and development and they're going to spend more time with their child than any of us individually or collectively are going to be and so supporting families and having them experience positive outcomes, not only helps families, but has direct benefits to children. So, documenting whether and how newborn screening and follow affect family outcomes is really essential for understanding long-term- consequences.

So, how did we get there? So, this was a long time ago, back in the nineties. Congress was concerned that early intervention and preschool programs for children with disabilities had no evidence based, and so they wanted to begin -- well, not a strong evidence based for the outcomes of the programs specifically, so they began by funding several longitudinal studies.

One was called NEILS, the National Early Intervention Longitudinal Study. It was a great project. It was sample of over 3,000 nationally representative sample of children who entered Early Intervention programs who were followed until kindergarten. We really needed a study like that, just editorializing, for our newborn screening. We needed

that kind of systematic, longitudinal follow-up investigation.

So, this was a funding to SRI International. I was a consultant on the project, and I lead the families' outcomes component. So, we published three papers over the first few years of that project in pediatrics, focusing on what are families' first experiences with Early Intervention, what are the outcomes for families at 36 months, and how do you model what effects families' outcomes.

And we know that formal supports the things we do as professionals are important. We've also clearly found that over the years many, many different studies is that informal supports are also critical to family success. We mostly did a study also looking at family outcomes in Early Intervention based on that database and did another database based on data we gathered from two states.

So, near the completion of the NEILS Study, the U.S. Department of Education then funded something called the Early Childhood Outcome Center. Again, like we don't have really clear agreement on outcomes for families for newborn screening, there is no clear agreement on outcomes for children or for families in

Early Intervention and the government couldn't prescribe states to all use the same assessment instrument for Early Intervention because just like newborn screening it's a state-based enterprise, but the National Center to help articulate what some of those outcomes might be and to help the U.S. Department of Education decide what things should states be recording every year in their annual report to Congress.

So, they asked us, the Early Childhood Outcome Center, and again, this was a collaboration of SRI International, Kathy Hebbeler and her colleagues. There were two activities: developing a set of child outcomes that could reported and then a set of family outcomes, and I and my team lead the family outcomes component.

So, how did we get there? I can't go into all the processes, but we didn't just close our door and think of what these outcomes might be. We engaged in a series of consensus-building activities, collaborating with a lot of different entities, individuals, and groups, through technical assistance, both to us and from us. Through research, and through recommendations. So, the first task was again to identify a broad set of family outcomes. We identified a range of stakeholders:

parents, advocacy groups, state agencies, and researchers.

We got input from all of these groups through a variety of different means: surveys, focus groups, conference calls. We had advisory boards; we did literature review. I'm going through this because this is the process, we'll be going through with assessing family outcomes of newborn screening.

And after many, many months of all of this we came up with five simple outcomes. At the end of Early Intervention, we would hope that families would understand their child's strengths, needs, and special abilities and special needs. They would know their rights and be able to advocate effectively for their children. They'd be confident in their ability to help their child develop and learn. They would have support systems and access to their community. So, an example of the overall item families can help their child develop and learn that knowing new styles of effective parenting that provide nurturing and stimulating environment, use special techniques to enhance learning, modify the home environment routines, et cetera.

So, after developing those outcomes, we published a paper in great detail describing the process

of how we got to those outcomes and what was the rational for each, and that's what we hope to have by the end of this particular funding period for this project is a comprehensive paper saying here's how we got to and here's what our recommendations are for family outcomes for newborn screening.

We went through then several iterations of how you would actually measure that and so we developed an instrument called the Family Outcome Scale. It was based on the five family outcomes, the self-report instrument completed by families. Of course, it would be very inappropriate for us to go in and say, well, I'm going to do an assessment of this family and see how they're doing from my perspective. It's from their perspective. We want to know how they're doing, so we developed items through an extensive literature review again and feedback from parents and professionals.

We had two different -- actually, probably more than two different iterations with modifications based on data and feedback. We published the initial version in 2006. We did a revised version in 2011. The instrument is posted on our website and it's now freely available in 16 languages. This is not something we sell. It's just something that's available and for

programs to use.

So, version one looked like this, and we had both in English and a Spanish version of it. This says when your child is growing and learning how much does your family understand about your child's development and we had a one to seven scale. One is just beginning, seven is we understand a great deal, and there were blank middle points there in case you thought you may be in between a one and a three.

So, that version was difficult for a lot of families to complete. And Melissa did a study showing that families are much more likely to report one, three, five, or seven than the interim points. Texas Department of Early Intervention programs funded us to actually do a revision of the scale, so we wanted to create a new format that would be easier for parents to use.

We wanted to revise and expand the survey items to provide more information that states could use in planning program improvement, and we really had not done a psychometric study of the scale before then, and so this was the purpose of this study.

So, this is the current version of the Family Outcomes Scale revised. You probably can't read

that, so I'll just give you the high-level picture of the black bars are the five family outcomes. The lighter lines are the items that go under each of those outcome areas, and family rate themselves on -- so like we know the next steps for our child's growth and learning and one in the continuum is not at all and the other end of the continuum is completely. It's an agree/disagree type of format.

It's hard to get much more quantitative than that, but that's really how the scale is organized and so on one page these are outcomes. The U.S. Department of Education really, really wanted states to report satisfaction data, so we developed in a second set of items on the second page here. We don't call it satisfaction. It's perceived helpfulness of Early Intervention and the set of items that we did with that as well.

So, what do we learn from research using the Family Outcome Scale and then the revised version? Well, first, as you can imagine, a lot of different things need to be considered when developing an assessment tool. How do you word the items? We did detail cognitive interviews where we set down with parents and went through each item and said what does

this item mean to you. If I asked you this question, how would you think about responding to it?

We have learned that it has very robust psychometric properties. There's wide acceptance across states now in reporting back to the U.S. Government. Families generally report positive outcomes, which is good, but there's variability. We know that family-centered practices, as I defined very early in the presentation, are highly associated with outcomes.

Unfortunately, as you would expect, but you would hope not to be the case, but race, ethnicity, and income and language still are related to variability and attainment of outcomes, and there's been great interest from this international perspective.

So, Melissa and I published a paper on measuring family outcomes, really talked a lot about all the complications in issues in developing such a scale. So, this is from a 2020 report. So, states are required to report family outcomes very year to the U.S. Department of Education and they include that in the report to congress. So, in this map it reports what instruments states are using.

So, some states are still using the original version because they can choose whatever they want to

measure the outcomes. They just have to report the outcomes. This shows there are some states that are using our original scale and some that are using the revised scale, so the purple states are all using the revised scale and the green states are using our original scale. So, you can see that, well more than half of the states are using this instrument, in one way or the other, to report their outcomes to the government.

There have been several international studies. Colleagues in Singapore did a psychometric evaluation of the scale in Singapore. A couple years ago there was a nice article from Australia looking at the predictors of family outcomes using this instrument from children with an autism spectrum disorder. Elizabeth and I are working on a paper based on longitudinal study of outcomes experienced by families who have a child with Congenital Zika Syndrome as part of our NICHD funded Zika Project. It's an interesting concept, though, to think about longitudinal analyzes because if you think about a longitudinal analysis of children, you would expect growth over time, right? And so, constant attainment of new developmental outcomes and you would expect, hope for an upward trajectory.

For families, it could be more of an up and down thing, so you think about, I know a lot about my child's disorder. You might know a lot about it at the beginning, when you first get information, you feel pretty confident about that, and then there's a new discovery made. And you go, wow, now I need to understand something different. And anxiety can be up and down as well, and so it's thinking about it from a longitudinal perspective is especially challenging.

So, here are our primary goals. I'm to what we're actually going to be doing here is to develop a framework and identify domains of assessing family outcomes for newborn screening like we did before. We're going to be using multiple sources of input and engagement to identify an initial set of outcomes. We're doing an extensive literature review, we're meeting with stakeholders from a variety of different groups, and we have an advisory board that we're establishing.

Once we come up with a draft set of outcomes, these will be posted for input from anybody. So, there will be a survey with opportunities for quantitative and qualitative feedback, there will be direct outreach to parent and professional

organizations, and we'll have ongoing advisory board feedback.

We'll finalize then a set of outcomes, the recommended outcomes, ideally endorsed by diverse stakeholders, and then we'll write an article, like we did before, describing those outcomes, the justification for them, and deeper rationale for each. We'll begin work then to determine the next steps in instrument development and application.

The funding is only eight or nine months for this phase of work and so we thought maybe we would have a draft instrument by the end of this project. We now realize that the community engagement that we need to do and the discussions we need to have identifying these outcomes and how they might fit into an overall longitudinal assessment like what you were just mentioning, Dr. Calonge, will be very important for us to think about.

So, there we are. That's where we are. Thanks very much for listening and for the opportunity to talk and I'll be glad to answer any questions.

Committee Discussion

DR. CALONGE: Thanks, Dr. Bailey. I wonder if you're willing to stand up at the podium while we have our discussion.

DR. BAILEY: Sure.

DR. CALONGE: I appreciate it. So, we're going to begin Q&A and Discussion. We're going to start with Committee Members first and then move on to our organizational representatives. For folks in the room, if you could either raise your hand or put your tents up so I can see it, I'll try to keep you in order, and I see you already, Jennifer. And then if you're online, if you find and use the "raised hand" feature on the Zoom screen, we'll call on you as well. And let's get started with Jennifer.

DR. KWON: Jennifer Kwon, Committee Member from Wisconsin. So, I'm really interested to look at the data from Wisconsin, actually. You've motivated me to do that. I was curious if there's missing data. There must be families who refuse to participate or don't participate but is there any way of tracking them to see -- and the reason I ask this, of course, is because of the newborn screening portion of it. That would be very important, right, as an outcome.

DR. BAILEY: And it's going to be more challenging in newborn screening, right, because Early Intervention is a national program, it's a single program, it has many different components to it. But it's a program where children are tracked for three years until they reach 36 months of and then they move into preschool Special Education programs and so there's a natural tracking process there. But families, it's voluntary for families to fill out this instrument and so there will be missing data for sure. Is that what you're asking?

DR. KWON: That's part of it. And you know, I don't really think of Early Intervention as being strictly a national program.

DR. BAILEY: Sure.

DR. KWON: That the administration is not only state-based, but it's county-based.

DR. BAILEY: Yes.

DR. KWON: And I think that many people who refer patients for Early Intervention have seen this directly, that depending on the county you live in, the services you get can be markedly different. And so, part of my interest in Wisconsin is really trying to see where those data live and so I think that -- yes, I' not

sure which would be harder, but it'll be interesting to look at. Thank you.

DR. BAILEY: In Early Intervention, yes, you're right. There are county-based programs within states. They all operate under the state's Early Intervention Policy Program and that program operates under national guidelines. It's just like newborn screening in the sense that the federal government has guidelines. It's a little stricter because there's a lot of money that goes to states for Early Intervention programs and to get that money they have to report, they have to submit all the data related to this report for Congress, so states have a lot invested in getting the data, but it's up to families to provide it.

And counties provide it to states, so it gets rolled up to states, and then states get the data and roll it up. There are just a few -- you only need to report three things to the federal government, so they roll up items for whatever surveys they use to answer those questions. But because with newborn screening we have a problem with follow-up already, you know, tracking families after three years is going to be a really, really big issue. Yes, thanks.

DR. CALONGE: Next, online we have Kamila.

DR. MISTRY: Thanks, Ned. Thanks, Don. That was a great presentation and very important work. I just want to follow up on something you said in your presentation around the variation that you found in terms of race ethnicity and other demographic characteristics or really even thinking of this a little bit broadly through an equity lens and maybe thinking about social determinants of health and other ways we can think about this.

How is that going to impact the way we think about the stakeholders who are coming to the table, and I just want to make that connection and also learn a little bit more about what you learned from your prior work.

DR. BAILEY: Right, so there's several things embedded within that question, so in terms of our prior work, we found that a lot of different factors affect family outcomes. And so, certainly, family-centered practices do, certainly what professionals do with families, but we have found that families from non-white populations and from low-income groups would statistically have lower outcomes, at least then did, and I'm guessing that's still going to be the case because of systemic inequalities and problems in

our system, just as you've already mentioned.

So, we're hoping for a couple things. One is to make sure that in the context of our engagement and outreach that we're engaging as diverse a stakeholder group as we can get to make sure we have the right inputs. It does raise an interesting question about whether the same set of items would apply to everybody and so we don't know the answer to that, but I think we'll learn some through our processes.

But gathering these data, and especially if we can do it in a standardized way, can ought to lead to program improvement. That's the only way you can really start making changes as the ones you described if you don't have the data to help inform that.

DR. MISTRY: Just to follow up really quick, I mean I think some of it is also through whether those questions in themselves are -- how do I say this? Are we asking the right questions and really critically thinking about that within that stakeholder period and making sure that we're asking questions that are valid to all populations, and I think that's where it's really important we do that and spend the time to make sure that particularly within the variation that you've seen.

DR. BAILEY: Right, and so you can do that

in a couple ways. One is through engagement with the input on actually developing the items, then secondly, doing studies that look at outcomes as a function of a variety of different factors. So, we found that in Singapore, for example, the psychometric properties worked very well, but in other situations we've found -- well, the psychometric properties in other countries seem to be working quite well, but the question of outcomes and how that relates to a program improvement across the nation is going to be really critical.

DR. CALONGE: Chanika?

DR. PHORNPHUTKUL: Chanika Phornphutkul, Committee Member. Thank you very much for the wonderful presentation.

DR. BRAILEY: Thank you.

DR. PHORNPHUTKUL: I wonder since many of the children who had newborn screening were enrolled in Early Intervention. Is there a way to look back a little bit to give us some clue or it's just too broad? Thank you.

DR. BAILEY: That's a really good observation. So, many children who've been, and as we reported earlier, many children with newborn screening

conditions actually do qualify for Early Intervention and many of them would be in Early Intervention programs. Getting access to that data would be really hard because the Early Intervention programs don't necessarily code the specific disorder and so whether they're eligible in terms of having a developmental delay or a condition that could lead to a developmental delay.

But that's an interesting point and I think, ultimately, and we've talked about this since the last meeting about trying to come up with some better ways to integrate newborn screening and Early Intervention. That could be one way to do it is look at those data systems.

DR. CALONGE: Michele?

DR. CAGGANA: Thanks for that presentation. Michele Caggana. I know that you've had some discussions with some of the regional genetics networks, but I'm wondering if you could just describe a bit like in real practice, boots on the ground, how you ensure that you're getting a true voice from families because we all know the families that we work with, but how do you find and engage those other families to give you a complete picture?

DR. BAILEY: So, that's an important question, right? So, we're working through some of the regional genetics' networks. They're organizing focus groups for us and potentially doing some surveys. We'll be reaching out to a variety of different parent organizations, but you're right, the people that are affiliated with those groups don't necessarily represent the nation at large. So, I don't have a good answer for you yet, Michele, but we are working to try to figure out how we would get as many voices as we can and then provide as much opportunity for input once we've done some initial development work.

DR. CALONGE: Shawn?

DR. MCCANDLESS: Shawn McCandless, Committee Member. I think my question is partly answered and partly not. I have two questions. The first is who do you define as the stakeholder groups because it seems to me that newborn screening is a different thing than Early Intervention where you've got people who are engaged in the intervention that that's your stakeholder group.

There would appear to be multiple stakeholder groups related to newborn screening outcomes and I would like to understand better the strategy for

defining and recruiting from each of those stakeholder groups. The second question is how do you propose to separate out, satisfaction around newborn screening from satisfaction around follow-up and care and management and early intervention and all the other things that happen after newborn screening?

DR. BAILEY: So, I'll take on the first one first because it's the hardest question, right? I mean because newborn screening, once you finish the lab work, it's a scatter shot, right? You go to this clinic or that clinic, you get services here and there and it changes over time. You've got your regular pediatrician, you've got specialized treatment services, it becomes not so much a system anymore and so how do you evaluate -- can you evaluate the system and at what point in time?

Are we going to say, okay, at 36 months and 24 months where are families who've been identified through newborn screening and are we evaluating their experiences with their specialty clinics, with their genetic counselors, with their physician? So, what we're trying to do is focus on, at first, outcomes irrespective of a particular service context and just say where are families now, right at this point in time.

It's going to be very hard to answer the question of evaluating the newborn screening system, right, because it's really not a system. I mean Early Intervention is hard enough, but it is more of a system than newborn screening it, at least over the first three years of life.

There are a lot of stakeholders too in Early Intervention. You think of physical therapists, occupational therapists, speech and language pathologists, early childhood special educators, case managers, counselors, family support professionals, and pediatricians, and so there are stakeholders there already. We're putting together an expert advisory board right now and so we have representatives from a number of the key stakeholder groups in newborn screening, but there are so many. How do we do that with all of those people? And so, in part, we'll be getting initial input, but the biggest thing is once we have an initial draft, it's just spreading the draft down as widely as possible through advocacy groups, through professional organizations.

The last time we did that I can't remember, so we got a thousand and something suggestions for items and we were doing Q source on the floor and looking at

how different items came together and really trying to understand it from different perspective, so your point is really well taken. Thanks, Shawn.

DR. MCCANDLESS: Shawn McCandless, Committee Member. Can you specifically tell us who are the groups that you're trying to measure outcomes within? Because what I've heard is a lot about individuals that have positive newborn screens and turn out to be affected with the condition of interest. It seems to me another obvious group that it would be very important for us to understand, is individuals that have a positive newborn screen, but turn out not to have an underlying condition for which the screening test was intended.

And then there's the larger group of individuals who end up having a negative screen and how do you propose or what is the plan for ensuring that there's adequate representation of all three of those stakeholder groups in the outcomes that you intend to find?

DR. BAILEY: So, I guess I would differentiate the outcomes themselves from the context and the populations and so in some ways the instrument we developed is very agnostic in terms of those kinds of groups and I would hope that this one would be

relatively the same so that it could be used in all three of those situations. So, you would want to know what the outcomes were for families who received false positive results.

You would want to know outcomes for families whose condition wasn't on the RUSP and who experienced having a child with a particular condition that could be on the RUSP in the future. Wouldn't that be really important data for the Committee to consider in terms of making decisions about whether adding a condition to the RUSP and I know that Aaron and Sara are going to be talking about this very issue of how do we weigh in -- as you know, I've been talking over the years about how do you bring in the family voice in addition to public comments? How do we bring in data about family experiences and outcomes to really help inform the decision this Committee makes.

DR. CALONGE: Jeff?

DR. BROSCO: Jeff Brosco, HRSA. And so, it might help with some of the context, Shawn, and then I do have a question. So, remember that - was it 20 years ago, that this Committee started talking about how we need to look at long--term- follow-up for what's happening with newborn screening. I think it was Alex

Kemper's paper back when he was a young man and since then there have been reiterations of his papers and more work. And we at HRSA have funded some long-term follow--up- programs in newborn screening and they're putting together some really interesting data and thinking about this.

You will recall that we presented this sort of three buckets of data where Carla and the CDC folks are in that first bucket, looking at analyzing data and the second is follow-up, and long-term- follow-up, where does that fit in? And we do hope at future meetings to be able to start saying what might that roadmap look like, but that's five or ten years out, right? Because as everyone has been pointing out, there is so much complexity here.

When we start thinking about what those long-term outcomes might be, well obviously, there's the individual child and systems--level things, right? So, maybe connections to Part C. -If you look at the way we follow the EHDI Program, the newborn hearing screening, the one 1-36 that everyone hears about, that six--month outcome is actually connection to Part C, so it's- a systems level measure, so we can imagine something like that.

In what Don and his team is working on is what is the outcome measure for families, and as you pointed out, it could be used in different context. It could be used in a research context, a continuous quality improvement approach, and we are agnostic to what that system looks like because it's still kind of a dream, but we're trying to move toward it.

And this all leads to my question for Don, which is I heard about outcomes. Are you also thinking about quality of life because you can imagine that just how families are doing inherent to themselves is a worthy outcome of newborn screening.

DR. BAILEY: So, that could end up being one of the domains for this particular instrument. We consider that in the Early Intervention Program, and it was the sixth domain at that time. We got huge pushback from states because they said we can't be responsible for families' quality of life, and isn't that an interesting response? But their point was that quality of life is affected by so many other things that to put it on the program was a challenging thing for them and so we didn't have it as a part of the instrument.

I couldn't agree with you more. I mean, that's really the bottom line, isn't it? Everybody

wants a good quality of life for families and a good quality of life for children. There are great scales out there. There's one item quality of life measure that you can use is highly predictive and so we could use something like that. But I think what you're bringing up, Jeff, is a broader question about what is the -- I don't like to use the word "battery," but was it the collection of measures that we would want to look at in terms of evaluating the system overall?

And what we're looking at here is a piece of that, so child outcomes might be even harder because you've got Condition A, you're going to be looking at one set of outcomes. Condition B, you're looking at a completely different set of outcomes. Here we hope to have a relatively standard set of outcomes that could be used across families, recognizing it's not going to work for everybody.

DR. BROSCO: Just a quick follow-up, because we at HRSA think about this a lot and if there are 13,000 conditions that make up children with special health care needs, coming up with individual child measures is surely impossible. But it may be that family outcome measures are kind of the universal common denominator that connects. So, if a child has cancer or

sickle cell disease or hemophilia, or methylmalonic acidemia type 1A, yes, they're all going to have different outcomes, but family well-being might be one that cuts across all. It tells you how well the system is working.

DR. BAILEY: An overall construct like understanding your child's condition that can apply to every one of those conditions you mentioned and everyone on the RUSP and you can come up with a way to assess that, the agnostic again, a disease agnostic in some ways.

DR. CALONGE: Christine, I'll get to you in just a minute, but I wanted to follow up on that because you came close. The issue about the value of improvement in the measurement on the scale, so the reason I bring that up is that ultimately, in my mind, somewhere down the line these measurements will feed into Committee decisions trying to balance benefits and harms and there's always this kind of unspoken harm about resource utilization and opportunity costs. And so, the question comes down are you already thinking about what is the value statement for an improvement in this score; does that make sense, because we do it for quality adjusted life years, right?

We have a number. Maybe it's not a very good number, but it's a number that's used in health care to decide what to fund and what to not fund. So, it's just a question. Do you see it translating to a value that we can balance in terms of other things the Committee looks at?

DR. BAILEY: I don't mean to be flip in this response or to avoid it, but to say that we're trying to focus right now on the development of the measure and then what you're just asking is about context. You can have a measure of quality-of-life years, but what is the meaningful quality of life years, right? And so, what we're trying to do is, first of all, figure out you measure it and then it gets fed into a system that says, well, for us to make a decision we really need to see this kind of change or this kind of status, so you start with the right measure tool.

DR. CALONGE: I only brought it up since by the time the Committee starts thinking about this, I'll be long gone. Christine?

DR. DORLEY: Sure, just a question that I have regarding the different states using several different surveys. Do you have any issues with data quality, and then what incentives are there for states

to transition to the survey that you prefer?

DR. BAILEY: So, there is no incentive for them to transition to our particular survey because the federal government can't require a state. What they require is them to report every year. There are three family outcomes that they report and so they can roll up the answer to those outcomes based on our instrument or based on any other measure, or if they can develop their own scale. So, there's no incentive right now for them to do that.

Now, in the new study, we had a standardized set of questions and those became the focus of a longitudinal study and so I think we have two really different kinds of questions here. One is what would ultimately be a reporting system for newborn screening programs? If there was one, when would this data be collected and so forth? And then, the other question is in the context of a research study. If you were going to really do a national newborn screening longitudinally study, you would have to have much more focus on reliability of gathering the data and using it in a systematic way with the same instrument.

DR. DORLEY: One other thought I had regarding your outcome. On your Survey Question Two, it

talked about we are able to find and use services in programs. There's a difference in being able to find a program, but then why don't you use it? And so, in the African American community, immigrant community there's a lot of mistrust because you have providers that don't look like they do. And so, is there any plan to delve into that a little bit more because that does affect health outcome because of access and not being able to in your community take part in that particular service.

DR. BAILEY: Right. So, I'm trying to figure out the best way to answer your question. I mean, I think again if designed properly the scale would describe whether or not they feel confident in finding services. But then, the question is what are the factors that influence -- and use could be another thing. We know how to use the services and we access them. What are the factors that contribute to some families accessing and using them and others not accessing and using them? So again, the tool becomes the vehicle for understanding the questions that you're asking.

DR. CALONGE: Bob, I think you get the last comment or question.

DR. OSTRANDER: Well, thanks. Robert

Ostrander, American Academy of Family Physicians, and it's good to have a family-centered morning here. Looking at your matrix reminded me a lot of Carl Cooley's medical home index from 20 years ago, which is my entree into this world. I was part of that Learning Collaborative for Children with Special Healthcare Needs.

From then forward, one thing I have heard from our parent partners over and over again that they value is that their good days being good days. In other words, their diagnosis, follow-up, and treatment program allows them to relax on their good days when they're just home hanging out and especially on their good days when they have special events planned. And I wonder if perhaps the notion of measuring quality of life might be better assessed by picking one or two narrow measures of quality of life and including questions like that.

And I was a little curious about the fact that you have a whole support system section and none of that has to do with the medical support system. It looks to me like the only medical question in there is medical and dental needs are met and I wonder if there should be some more expansion of what medical needs are means in terms of family outcomes. The parent partners,

this isn't my brain, the parent partners I worked 23 years with this, told me that's one of their key things is being able to relax on their good days and if something goes south, they know who to call and it's going to get taken care of.

I'm going to throw in a quick second question just for thought, and that is I'm from a little, tiny rural area in the DEIJ world. I think "rurality" is the word that's coming out, needs to be considered as well because it doesn't get assessed in terms of the disparities that those in rural areas face when people are focused on the other areas of disparity. Thank you.

DR. BAILEY: All the questions that everyone has brought are really important and they point to the complexity of actually what first might seem a simple task is not simple at all. Your comment about the medical components, it's like that that will be more salient in the newborn screening context than it is in the Early Intervention context, and so we'll see what we learn from the gathering of the data process.

Your good days and bad days comment made me think a little bit about some things we've wrestled with, with the instrument itself. So, since it's a

parent's perception the day they fill it out is it a good day or a bad day and how that affects their reporting. Because I know I go through days where I feel like I'm in control of things and the next day I'm like, oh my gosh, so there are measurement issues and around both timing and subjectivity of the skill that are going to be really important to think about. It's not going to be a prefect instrument by any means, but we have to start somewhere, I think, because we have nothing now.

DR. CALONGE: I hope everyone will join me in thanking Don for an excellent presentation and discussion.

DR. BAILEY: Thank you.

(Applause)

DR. CALONGE: As he sits down, I want to point out that Dr. Kemper will always be young to me.

(Laughter)

Families' Search for Meaning and Value in Rare Genetic Diagnoses

DR. CALONGE: Now, we'll have two presentations focusing on research related to family

perspectives. Both of the presentations serve as examples of the kind of research the Committee could use during evidence reviews to better understand family and other benefits for population level screening of new conditions. Examples would be especially relevant at the end today when we start discussing the kinds of evidence that the Committee can consider when reviewing that benefit on specific conditions.

First, we will hear from Dr. Sara Ackerman from the University of California, San Fransico. She will be joining us virtually. Dr. Ackerman will be sharing her research on families search for meaning and value in rare genetic disorders. She's an Associate Professor of Social and Behavioral Sciences at the University of California, San Francisco, and is a medical anthropologist work in the interdisciplinary fields of empirical bioethics and implementation science.

Her research draws on ethnographic methods to examine social, ethical, and equity issues in genomics. Dr. Ackerman also investigates parents and community members' perspectives on health data sharing and the feasibility of participatory data governance models. With that, I'd like to turn things over to Dr.

Ackerman. Welcome.

DR. ACKERMAN: Thank you so much. I hope everyone can hear me. I'm going to share my screen now so you can see my slides. Hopefully, everyone is seeing my regular slide deck here, let me know if not.

DR. CALONGE: We can see it. Thank you.

DR. ACKERMAN: Great. Thank you. It's so good to be with you all today. Thank you, and thank you to Dr. Brosco, for inviting me. I am going to be talking about families' experiences today. And in particular, I'm going to be focusing on the question of utility or the value of genomic sequencing for children with rare conditions that are suspected to have a genetic etiology, and I want to acknowledge right off the bat, that whether we can even use the term "diagnostic" in genomics is contested.

A clinical diagnosis is very different from etiological information generated through a molecular level analysis, so I just want to say that right off the bat. Our team used the term "diagnosis" a lot, but didn't always group them, so that's something we can talk about.

I'm going to consider current definitions and approaches to understanding utility and then I'll

share some of the findings from a study that we did with diverse families undergoing genetic sequencing. I'll conclude by suggesting that an expanded conceptualization of utility can help us understand the full scope of what matters to families and will enable us to assess whether potential benefits of diagnostic sequencing are likely to be equitably distributed.

So, existing definitions of utility are usually presented in a binary, so if we think about emerging genomic technologies, they're usually assessed based on clinical utility or how they inform clinical care and health outcomes. Of course, also important, particularly in my area of research is personal utility and what we indicate by this is the effects of these new technologies on the lives of individuals, in children, but in particular, on how people think, feel, and behave after they've received genetic information.

So, I put a red box here around this social dimension of personal utility. This includes the impact of genomic information on social support access, experiences over fear of discrimination and also access to nonclinical services. So, this is really where we get into families' day-to-day lives in efforts to care for their child, but unfortunately this category of

personal utility has received a lot less attention from researchers, particularly, in terms of the experiences of underserved and disadvantaged families who have a child with a suspected genetic condition.

So, in an essay that's hot of the presses and co-authored by Dr. Aaron Goldenberg, who'll be speaking after me today, the idea of middle ground utility is put forth as a way to shift attention to the potential benefits of genomic testing that fall outside this conventional binary I just described. So, this encompasses the sort of neglected social utility category I just mentioned, in particular, the services provided by Special Education teachers, occupational therapists, and other community-based providers who are usually outside of the mainstream clinical arena.

You know families know well the complex service landscape that they and their children's special needs enter into and here I have one parent's depiction of the many service neighborhoods, if you will, that they navigate. And I want to thank Cristin Lind for allowing me to use this image, which she calls "care mapping." So, it's very hard to see, I realize, and I think that's part of the point.

But in the lower left, the blue area is

medical system and genetics is just one small bubble, among many, and there are other domains, of course, including developmental assessments, school, advocacy and leadership, recreation and community, legal and financial, and social support. So, most of the work coordinating care across this very complex, loosely connected network of agencies, organizations, and informal groups falls on parents and caregivers, but at least in the research world we don't know much about the journeys of families through this care landscape, especially underserved families.

So, the real question here then is what role does rare genomic diagnosis or etiologic information play? As families try to navigate through complicated service landscapes and I think that qualitative approaches to understanding this early is essential to help us answer this question because it allows us to have in depth engagement with families, both outside the clinical setting and over time.

This brings me to the empirical work that I'll be sharing with you today and this is based in the Program in Prenatal and Pediatric Genomic Sequencing. Our acronym was P3EGS. This is a study that to place at the University of California-San Francisco from 2017 to

2022, and we're still analyzing some of the data.

P3EGS was one of six clinical sites in an NIH consortium called CSER or Clinical Sequencing Evidence Generating Research. It was the second iteration of CSER. And a primary goal of the consortium was to recruit a high proportion of participants from populations that have been historically excluded from genomics research, including underrepresented minorities and medically underserved populations. So, the NIH mandate was for sites to recruit at least 60% of people who could be classified in these categories.

The aims of the P3EGS study were to examine the clinical utility of using exome sequencing for children who had previously undiagnosed either neurocognitive or congenital conditions that had a suspected genetic etiology, as well as pregnant women with a fetal anomaly detected by ultrasound, and this was one of the first studies to do prenatal sequencing.

The second aim was to explore ethical and social issues in returning rare etiological information to diverse families. We had recruitment sites in San Francisco, Oakland, and Fresno, California, and you can see the number of families recruited at each site. There were significant challenges in recruitment in our

community settings at the general hospital in San Francisco and Fresno. Happy to talk about that later because there's a lot to say there about the research capacity with our community partners.

Here is the overview of our families who enrolled. We had 845 families total, 529 of them were in the pediatric arm. I'm going to be focusing specifically on our pediatric arm mainly because the study populations are really different demographically, as well as what we learn from families in terms of pregnant women undergoing sequencing versus families with children; but we do have quite a few publications coming out on our prenatal families' experiences.

So, in the pediatric arm, 82% of our families were covered by California's Medicaid program MediCal, and I think this is an indication that many of our families were economically disadvantaged. The families were also very demographically diverse in terms of the languages spoken as well as self-reported race and ethnicity. -And our Hispanic-Latino families comprised about 40% of our pediatric population.

Our ethics team conducted an ethnographic project to understand families' experiences as they enrolled in the study and received results, as well as

after they received results. And for those of you unfamiliar with ethnography, it's an approach used by anthropologists and other social scientists in which researchers really try to emerge themselves in a particular setting in order to observe behaviors and interactions up close and understand cultural phenomenon from the point of view of the people that we are studying.

We conducted observations, both at the enrollment time period, as well as during results return and we conducted longitudinal interviews with parents after they received the results and then again six months later to understand what their ongoing experience was, and we focused, in particular, on expectations of genetic testing. Many of these families had never done any genetic testing before, although many had been on a long diagnostic odyssey, their understanding of the results they received, any health and other related decisions based on learning the results, and also their day-to-day lives and social context.

So, we conducted a total of 61 interviews with 32 families. 40% of our interviews were conducted in Spanish. We did speak with mothers, fathers, and caregivers, and sometimes the children themselves wanted

to participate in the interviews and that was actually really rewarding to us to talk to a whole family. Mothers were more likely to participate than others. And we also observed 49 enrollment and consent sessions and 53 return of results sessions.

I want to emphasis here that in considering who to interview, we decided to oversample for families with positive results. And what I mean by that is families who received etiologic information that pointed to a likely genetic cause of their child's condition. We were very interested in understanding the impact on families of learning that their child's condition had a genetic explanation, but we also wanted to talk to families who received inconclusive and negative results, so that was about half of our sample. And on the right, you can see the overall results from the pediatric population. Far more people received negative and inconclusive findings.

Now, I'm going to turn to what we learned from families about the utility of genomic information. There's so much to say here, so this is a snapshot. But in addition to seeking an explanation for their child's condition, many parents told us they were also looking for information and assistance that would help them

better care for their child on a day-to-day basis.

When asked what she expected from exome sequencing when enrolling in the study, one mother said maybe if there was something that no one was trying to help me with and that she needed, number one, is school. And similarly, and this was during an observation of an enrollment session, a mother who is considering enrolling in the P3EGS Project asked our ethnographic team, and we had to defer this question to the clinicians, but asked whether enrolling in the study would help the family qualify or IHSS or in-home support services, which is a state-sponsored program that pays for homecare services for older adults and disabled children and they had not qualified previously, so she was hoping that an etiologic diagnose would help. She ultimately decided not to enroll in the study.

We also learned that parents and clinicians became partners in creating value and this really points to how utility is a relational phenomenon. So, families' interactions with clinicians learned to lower their expectations of a diagnosis, that a cure or improved treatment options was quite unlikely, that pursuing further knowledge was good parenting. They learned to absolve themselves of any guilt they carried

that it was their fault, or their child had inherited the condition from them, and they also learned to have faith in what genomic science might learn in the future and to defer their hopes for the present.

And so, this parent's quote really sums up the sentiment. "We don't know exactly yet what he has, but we're on the right path." We found that for many parents' etiologic information prompted a lot of relief, even if what they learned did not provide a complete answer. So, one child who had an autism diagnosis and shorter statute the mother told us it definitely answered the growth issue, so there was a genetic variant returned to them, but there really wasn't any known genetic etiology of the child's autism.

But on the other hand, a lot of parents told us they were very frustrated. The parents who received a positive result even sometimes said that such as this example, who these parents said they haven't helped us at all. We just have a name, but we don't know what it means. And what they're referring to in terms of the name is the name of the gene. So many of these results are so rare that it's a gene name about which very little is known, other than it probably explains the child's condition.

And another issue for a lot of parents was they would receive either a negative or an inconclusive result and they were frustrated because they hadn't heard back from the research team about the possibility of re-analysis. So, this mother said, "I'm kind of waiting for your team to let me know once you have more information in terms of that specific mutation as more people get testing done." So, this is a real issue with families enrolled in research who are hoping to benefit from developments in genomic science. But after the study ends, especially families without insurance willing to pay for additional genetic testing, what happens to these people.

So, we found that for some parents a genetic diagnosis did facilitate access to community-based services. The mother of a two-year-old, and important to mention that the result for this child was associated with a well-known syndrome, told us that this diagnosis helped her child get into Head Start and that the genetic information really kind of prompted that, so this was a success story for her.

Other parents, on the other hand, and we found this to be a more common story, especially with our socioeconomically disadvantaged families, that they

really struggled to use genomic information. So, one mother of a five-year-old whose result was not associated with a known syndrome, it was a rare variant, said even though I took the genetics papers to the school, they didn't pay much attention to it. So, her efforts to improve her child's access to Special Education did not succeed.

And another mother similarly told us -- she said it did not change the clinical diagnosis, it did not change the IEP, but it did create sort of animosity between me and the school district, so there was sort of a mismatch in the parent's expectation and what the school was actually able to do with this rare genetic information.

So, we've really ultimately found that families' ability to realize what we might of as middle ground or social utility were shaped, in part, by the type of result, and there's some indications that syndromes of known behavioral traits in developmental trajectories are more translatable to the service sector than rare variants that, as yet, are not associated with well-characterized syndromes.

Also, how long a child has been in the system seems to matter a lot. So, prior assessments and

clinical diagnoses seem to really have a lot more sway than rare genetic information. And we also found that families' ability to advocate for their child and to use etiologic information that effort is really shaped by how well they're able to mobilize certain knowledge skills and resources, and we call this cultural capital, and its unequal distribution really puts socially and economically marginalized families at a distinct disadvantage. So, our concern is that the potential benefits of a rare diagnosis may be inequitably distributed.

I just want to conclude by encouraging to shift toward a more expanded, multilevel conception of utility, which really can be understood as produced through these dynamic interactions between families, clinicians, health care systems, schools, and other organizations, as well emerging technologies such as exome and genome sequencing, as well as health and social service policies.

So, it's some questions that I think need answering include what role does genomic information play in families' ability to access services and their day-to-day lives, as well as their overall well-being, are schools and community-based services able to use

genomic information alongside functional and clinical assessment, particularly these very rare diagnoses are starting to be generated more now that we have access to exome and genome sequencing. And finally, how do federal, state, and local policies shape the meaning and actionability of genomic information?

And I think it's very important that we answer these questions for all families, and specifically do emerging genome technologies mitigate or exacerbate existing disparities in access to services. So, I also just really want to thank all the families who spoke with us. And what I'm including here are some screenshots of the comic book styled story we created in collaboration with an artist-health educator at Booster Shot Media and some of the families who are enrolled in P3EGS.

And in this story, we depicted a fictional family undergoing exome sequencing and we brought in a lot of the themes that we learned from our interviews with families with the goal of explaining to families what we learned in the study and thanking them for participating, and we sent this comic book out to the families last year. And I also want to acknowledge the P3EGS research team, in particular, our Ethics Group.

So, thank you so much, and I'll stop sharing now.

DR. CALONGE: Thank you, Dr. Ackerman. I'm hoping you can stay with us a little bit more until after the next presentation and be present for discussion and questions. This is such critical work, helping us catch up with understanding what we should do with the technology now that we can do it, so this, I think, has lagged behind our technological advances and so filling in that gap is just critical.

The "Value of Values": Expanding Assessment of Net Benefits and Harms through Social Science Data

DR. CALONGE: Now, we're going to hear from Dr. Aaron Goldenberg from the Case Western Reserve University School of Medicine. The title of his presentation is The Value of Values: Expanding Assessment of the Benefits and Harms Through Social Science Data. Dr. Goldenberg is a professor and vice chair in the Department of Bioethics at the Case Western Reservice University School of Medicine. He's also Director of the Case Western Bioethics Center for Community Health and Genomic Equity. Dr. Goldenberg has a background in bioethics, health behavior, health

education, public health ethics, and public health genetics.

He has focused his work on the ethical, social, and equity issues associated with the integration of new genomic technologies into research, clinical, and public health settings. Dr. Goldenberg.

DR. GOLDENBERG: Thank you. It is such an honor to be with all of you and to be in person. I will not let the Lions' loss from last night reduce my enthusiasm for today's conversations, but there are lots of families in Detroit having a sad day today.

So, thank you, Dr. Calonge, and Dr. Brosco, for inviting me and it's just great to be with the Committee and to be with all of you. My hope is that through this conversation and through these slides I'll turn our attention a little bit to methodological questions, to some theoretical questions about how we can take families' experiences, how we can listen to families and integrate that into our considerations, whether those are for new conditions, whether those are for the kinds of support structures that families need, but really to think about the value of social science data in these conversations in what I'm calling the value of values.

So, this slide is not going to be dissimilar to many slides that you've seen in the past talking about the concept that newborn screening is on kind of the cusp of really translational change, both in terms of the kinds of conditions that are be recommended or kinds of conditions that are being nominated, potentially later on set conditions, more uncertainty with particular conditions, the potential use of genomic screening and then, of course, the questions surrounding what happens to data and samples after are all putting us in a situation where we start seeing the future of newborn screening to have the need for a lot of changes, a lot of different ways of thinking about the work that we do, while also trying to preserve the benefits of screening for families.

This is where, I think, social science data is going to be incredibly, incredibly crucial and the problem is, as you've heard from our previous two speakers, there's really a lack of data pertaining to family perspectives, particularly both parental and public perspectives related to the kinds of changes that we're talking about in newborn screening and what data is there, which there is really amazing data out there I think is underutilized.

It's vital that we have data from stakeholders to both manage expansion of newborn screening, changes in newborn screening in a really transparent manner that maintains the ethical justification of newborn screening. And as was mentioned in the last session, to maintain trust in the system. We talk a lot about trust and trying to get families and communities to trust us, but I know one of the things that we've talked about a lot recently is really changing that narrative from one of trust to one of trustworthiness and how do we create programs that maintain our trustworthiness so that families and communities continue to benefit and continue to feel trusting in what we're doing.

And so, I think, as we're talking about expanding notions of benefits and harms in newborn screening, the kinds of data that were presented in the previous two presentations are exactly what we need to be hearing, not just about the benefits and harms to individual newborns, but also to families and society, and we need really complex and deep data to be able to do that.

So, what'd we mean by assessing values, and these are just going to be some questions that I think

we need to be talking about together. So, whose values, whose perspectives, whose concerns, whose expectations are we thinking about? Are we only hearing from parents with children with a particular condition? Are we only hearing from the public, generally? Are we hearing from parents? We need to have a lot more precision about who we're talking about when it comes to these kinds of data.

What are the values about? Are they about screening a particular condition, is it just generally about newborn screening issues, is it about newborn screening disparities, or access to care, something that we've talked a lot about on this Committee over the last few sessions. When are talking to people, is it during a pilot stage for a condition, is it in states that are already screening conditions and what families' experience has been like after getting screening, or are we talking about an activity that may be goes directly hand-in-hand with the evidence review process that we could think about social science data that might be part of an evidence review itself.

How are we actually getting information from families, are we doing through surveys or interviews with individuals and families, are we thinking about

focus groups or small group dialogue sessions? There are lots of innovative approaches, including ethnography that we just heard from the last session, deliberative democracy sessions that some of you maybe have participated in and other innovative approaches?

The question that's on the table for all of us is why are we doing this? It is to improve the matrix. It is to improve our evidence review process to impact the final score for this Committee's decision of yes or no for a particular condition, or is it to impact the ways in which the Committee's recommendations for things like state resources for parents or for clinicians or for choices of variants or how we return results? Is it more process oriented, is it about other recommendations for the kinds of resources that we think families will need post-streaming, is it about access or follow-up, is it about education or potentially consent for some conditions?

I think part of one of the things that is a big part of our conversations in some of the social science work in newborn screening is this question, which his as we expand do we start thinking about parental authority differently, do we start thinking about the mandatory nature of newborn screening

differently in order to give potential families choice around particular conditions. That's a hard conversation to have, but one that I think that we need to hear from families about before we move forward.

I think, for me, there are three problems in using these kinds of data in newborn screening. The first one is that newborn screening harms and benefits to families raised in Committee meetings, in other meetings, in lots of different things tend to be anecdotal or hypothetical. We worry about particular harms, we talk about particular harms, but we don't have enough data to show whether or not those harms are actually real and tangible and are experienced by families.

The burden of proof, I think, has been kind of historically higher for benefits and I think maybe we need to be rethinking the way we think about the burden of proof for harms as well. And the problem here is really there's just a lack of data. We don't have enough data on these kinds of harms or benefits from expanded newborn screening, for example. The second challenge is that when we do have data many times that data is dismissed as anecdotal or nonscientific.

Many people who don't know social science

research or haven't worked in social science research may not think about the data that we're presenting, both qualitative and quantitative data in the same way that they do other kinds of clinical data. And I think the problem is maybe a lack of understanding of what social science data is or how it can be helpful.

And then the final one is even when it is appreciated, when data on harms or benefits to society is part of our considerations, they're not systematically integrated into the evidence review problem, so the science itself doesn't actually get into our final decision-making process.

So, across these three, either there's not enough data, the data is dismissed, or the data is included, but not actually systematically included in evidence review. We have a real problem of not getting these family voices, these family narratives, these families' experiences into our considerations and I think in measurable and robust ways.

So, I'm going to give an example from Screen Plus. This is a comprehensive, flexible, multi-disorder newborn screening pilot program that we've heard about on this Committee before. PI'ed by Melissa Wasserstein in New York. It's a consented pilot, running in

conjunction with the New York State Screening Program. The goal is to enroll 100,000 babies at a high birth rate, ethically diverse hospitals over five years in the New York City area.

The goals are to assess the analytic and clinical validity of multi-tiered screening for a fluid panel of multiple disorders. We've heard about that study multiple times, but what I'm going to be talking about is this last part, which is assessing the ethical, legal, and social issues from parents' feedback, including interviews and surveys of parents who have enrolled in Screen Plus.

So, all parents who enroll in Screen Plus get an opportunity to participate in further surveys or interviews, either about their experience with Screen Plus or about other newborn screening issues. And we're trying to create a stable platform to hearing from families, both who have screened positive for a condition, but also of families who are just enrolled in Screen Plus, their children are negative for any condition, but whose voices may still be important to hear from on big, newborn screening issues.

So, the ELSI components of Screen Plus fall into three different categories. So, there's a consent

feedback survey. This is really about the research itself. We hear from families about what they liked, what they didn't like, why they participated -- actually, why they maybe didn't participate in Screen Plus, and that helps us to build further research opportunities and think about improving research.

The second two are really what we're talking about today, which are quantitative parent surveys. Families get this about one month after they receive their results from the study. It includes right now three surveys. One on expanded newborn screening and various newborn screening policy and program issues, one on dry blood spots -- so there's actually two studies on expanding newborn screening and one on dry blood spots.

We're working on a whole genome sequencing survey right now, but the idea is over a course of three to six months families receive two to three surveys, so they can choose to participate as many times as they want and in as many surveys as they want and give feedback on a variety of newborn screening issues.

We also have a component in the qualitative realm as well. So, approximately six to two months after birth, families who have received positive results

from Screen Plus will be entered into a qualitative data collection process where we're going to be hearing from families and hearing their narratives about their experience with newborn screening, about their experience with getting positive results at a much more in depth, interpersonal level.

These are going to be an hour, hour and a half-long interview and the idea is to hear their stories, to hear what their experience was like. And in a second, I'm going to talk about why I think it's so important to hear both quantitative and qualitative data. The kinds of things we're going to be talking about, as I said before, so we're going to be asking parents about consents, dry blood spot retention, newborn screening expansion, including what types of disorders we might want to screen for in the future, including age of onset, treatability, diagnostic and prognostic uncertainty questions, and issues related to newborn screening that may fit a little bit outside of our core kinds of questions, but things like trust in government entities, trust in newborn screening programs, issues around equity and diversity, and what kinds of information should generally be returned from screening results.

Our goals in all three of these data collection processes are to do a few things. One is just to inform newborn screening implementation to think about meeting family needs and what kinds of resources may be necessary and to hopefully impact newborn screening policy and newborn screening research. Those last two are interesting ones because they tend to be harder when it comes to integrating social science data into newborn screening policy development.

So, I want to talk, just briefly -- this is not meant to be a data presentation, but I'm an empirical researcher. I always have to show a little bit of data. So, I want to start by talking about the reason why I think it's so important to include both quantitative and qualitative data when considering social science research in newborn screening.

Here's some data from one of our studies, looking at parental attitudes towards various ages of onset, attitudes towards adding conditions with variable ages of onset to newborn screening, and we ask whether or not they thought adding particular conditions that had either an early, late, an adult onset, or conditions with no cure or treatment would be a positive thing, a negative thing, or neither positive or negative. And as

you can see from this very quick snapshot, a majority of parents thought that receiving information through newborn screening about conditions that might have on early onset, a late onset, or an adult onset tended to be a positive thing.

There were some families that said they were neither positive nor negative, and there were a few families that said this was a negative thing. There were about 225 families in this survey, but this is the danger of data like this. We look at a screenshot, we look at some statistics, and we try to think about how that might impact policy without better understanding the nuances of how families feel, what families are going through.

When thinking about these issues we're missing important details about their experience, about their voice, about their lives. These kinds of screenshots, these kinds of data are incredibly important to start, but they really have to be the start. Once you start looking at in depth data from families' experience, we see the nuance, the complexity that takes places in these issues for families.

So, here's a few quotes. "Whether the treatment is available or not, it's always preferable to

know if there's an issue." Someone else said, "I have a genetic condition that was not diagnosed until adulthood. I think it would've been very beneficial to know at a younger age."

But we also heard from some families that said, "Prior to having children, I would've felt that newborn screening for any disorder would be positive. Now that I have a child, I'm not sure I would want to know that information about a disorder that may or may not affect my child for several years or into adulthood, if at all, especially if there are no treatments or currently anything that I could do differently to lessen the severity or delay onset," right?

So, the reason why I think it's important to have this nuance data is to better hear from families and better understand why our policies also need to reflect that complexity, also need to reflect that nuance.

Context, context, context, one of the things that we really wanted to talk about today is how important how we ask questions to our final product, to our outcomes, to what we're including in our data. So, first, this is some data showing families' attitudes towards getting newborn screening when there's some

level of uncertainty. So, we asked families would you want a newborn screening results in cases where a child is at high risk to develop a serious condition that might need treatment, but doctors cannot tell when they will get sick, so potentially later onset. 92% of parents said they either strongly or somewhat agreed with wanting that kind of information, while 8% said they disagreed with that kind of information, so with that kind of uncertainty.

We also asked would families be interested in receiving newborn screening results for conditions where doctors could not tell whether their baby would have a serious condition and you can see a slightly different answer, 70% still strongly or somewhat agreed with getting that kind of uncertainty back, but it's thinking about these different kinds of uncertainty is important, right?

Are we talking about uncertainty with age of onset or are we talking about uncertainty with regard to actually having a condition and we saw some potentially really interesting differences between parents' attitudes. Context is important if we think about what population or what community or who we're talking to. Take that first question again, would you want to get

your baby's information regarding results that, for example, where a doctor might not be able to tell you whether or not you have a particular condition.

Our white families in our study we saw 60% felt hat they either strongly or somewhat want that information, while 40% said they strongly or somewhat disagree with the statement that they would want that information about an uncertain future condition.

When we look at our non-white families in the study, that number was statistically significantly different, where 80%, a much higher number of families, non-white families, wanted that uncertain information, right? Interesting finding, I think tells a little bit of something about where we might see some trends with regard to acceptability of uncertainty, but we need to get deeper into that and we'll go to that in a little bit.

How we ask questions also changed what kind of data we get. So, in the first column here, we say I would like to get my baby's newborn screening result in cases, again, where my doctor could not tell me if my baby has a serious condition back to those original numbers. But in a second survey, we asked people whether or not for uncertain conditions whether or not

they would think all babies should be screened in a mandatory fashion or whether or not parents should be able to give permission or should actually be required to give permission, and that number changed drastically.

We had about a 50/50, about 50% of parents said they were fine with a mandatory screen for conditions that had high levels of uncertainty, while the other 50% said, no, if there's that level of uncertainty parents should have to give permission in order to receive those results. We need to think about how that changes the way we talk about screening.

And then, finally, again context with quantitative versus qualitative. So, 70% said they would want uncertain information about a future condition, but again, very quickly because I know my time is running out, we see very different opinions when we actually look at more qualitative, in-depth data from families. This person said, "The only thing that I would hate to add to a mom is additional worry. If there's any uncertainty about the serious condition and no possible treatment, it's honestly better to live in ignorance and enjoy your baby versus always being worried and then one day they might get sick."

Someone else said, "Multiple doctors' visits

in early babies' lives are very stressful. Knowing that that might be coming or that there's a diagnosis would be valuable to help manage that uncertainty," a slightly different opinion.

"The more information we have the better. There are so many things that we don't know and can't predict about our own bodies and having the opportunity to know more about babies' health and probabilities is comforting," right? Again, this is all to show, that the importance of embracing the complexity of these kinds of data.

So, how do we move forward, how do we move forward on these things? So, let's go back to my original challenges. So, Challenge One is the fact that we just don't have enough data and that the data that's sometime presented is either antidotal or hypothetical. We need to work together to co-create research questions, whether that's the Committee with our advocacy organizations, whether that's state programs with parents, we need to work together to create questions that I think can move us forward.

We need to develop research that includes LC and social science methods, and we need more funding. A lot of funding opportunities in newborn screening

exclude the kind of work that we're doing, exclude social science data. For Challenge Two, how do we make sure that data is not dismissed as nonscientific? We have to create new opportunities for presenting and integrating social sciences like panels like this, really appreciate being able to have a panel like this and develop training opportunities in newborn screening for programs to work with social science date. I think there's lots of amazing training opportunities.

And finally, this is probably the hardest, how do we make sure that data is actually systematically integrated into our evidence review? We need to further develop decision metrices for these kinds of decisions that integrate value in social science data more effectively and it may be that these data are not meant to say this is to decide yes or now screening a particular condition, but thinking about how we can inform processes.

What kinds of resources do parents need, what kinds of things are of concern to families? Addressing Challenge Three is going to be the hardest. I think this is going to be one of the challenges for the Committee moving forward is how can these kinds of data be integrated. The reality is you're always going

to have divergent and pluralistic views among parents, right? You're always going to have a parent who is very concerned about uncertainty. You're going to have some parents that are more comfortable with uncertainty.

That's not a failure of the data, that's just a reality. That's the reality of families. Experiences that you're going to have this kind of divergent views, so we need to find better ways to include those divergent views. We need to think about determining thresholds for potential harms more effectively.

We need to think about weighing and screening versus clinical harms and what that means in terms of families' experiences. We need to value data that may indicate not just whether or not something should be screened, but whether or not it's about improving resources. And finally, we need to consider how we hear from families, and think about permission.

So, I want to end by talking about two very, very quick things. One which is that we need to think about not just ways that we can appreciate social science data, but ways that we can really improve the data that we're integrating. This is some core principles from Arthur Lupia, he's a wonderful political

scientist at the University of Michigan who does a lot of work on how do you improve and include social science data in policymaking and he really talks about four core principles that I think we can use as a benchmark for the ways in which we consider these kind of data.

The first one is rigor. How do we know what we know? The ability to be able to explain how we're understanding complex issues, especially when they're divergent questions, when there are controversies, when there is disagreement among Committee Members. We need to think about rigor and how we include these kinds of data.

Of course, ethics and ethical research, how do we make sure empowering our participants and our families to feel comfortable talking with us about their experiences. We need precision in measurement and conceptualization. If seven of us are doing research and all seven of us have different definitions of harms, that's going to be very hard to integrate into what we do on a daily basis here, so we need much more precision and shared conceptualization of things like benefit, harms, disparities.

And finally, causality, if we think about correlation and we see disparities, for example, in

outcomes in newborn screenings between white and non-white families, some data that's been represented here before, we need the ability to think about what's causing those disparities. If we're going to solve problems like disparities in newborn screening, we really need to focus our efforts on really improving our understanding of causal features and causal nature, causality for those disparities.

And finally, let's not reinvent the wheel. There are many of us in this room, there are many of us online, there are many of us in the world who've done really amazing work in this space, and I think we need to maybe do a better job of recognizing the work that is already out there. For example, many of us in this room worked on a paper just a few years ago on evaluating harms in the assessment of net benefit and created a new framework for thinking about harms, not only to individual newborns, but to parents and families.

This project was meant for us to think about expanding the ways in which we think about social science data, the ways in which we think about harms and how we can expand our notions of harms and our definitions of harms, and I think we should be pulling these papers back out and really thinking about them in

the work that we do. We don't have to do this alone, we don't have to this without some amazing work that's already been done, and I think that's an opportunity to do that and to hear from families who've already dedicated so much time into talking to us about their experiences.

So, I'm going to end there. Happy to open it up to questions for both Dr. Ackerman and me. I want to acknowledge the Screen Plus team and ICHD for funding this project, as well as our industry partners and many of my colleagues who have helped me think through many of these issues as well. Thank you so much.

DR. CALONGE: Thank you. That was great. You got me thinking. I'm going to start with maybe less of a question, but more of a comment. GRADE, do you know GRADE? GRADE is a evidence to a decision framework for evidence synthesis in recommendation creation and they have created a model that's been lightly used called GRADE-CERQual, which is an approach of trying to marry or bring together different data streams, marrying both the quantitative and the qualitative in going from the evidence to decision framework.

On a NASEM committee I chaired, we used that, plus another emerging area, which maybe you're

already doing, which is qualitative data synthesis, which is saying, now I'm going to combine data across qualitative studies, which is pretty well established in Europe, but just kind of coming to the U.S. now. And I'm thinking about that study because it thought about how to incorporate many different kinds of data streams in the evidence to decision framework, and something -- Jeff, we might ask if the statement is task is not already set for NASEM, that could they expand the statement of task to look at the use of GRAD-CERQual or other integrative data stream evidence to decision frameworks that could make sure that we're not excluding this.

The only reason I bring it up is because it does what you're talking about, the way you're talking about doing it, in a structured way. I can't tell you, Aaron, that it's the right structured way, but it is a structured way and I think it would be used. So, that was my comment to get us started.

DR. GOLDENBERG: I totally agree. I think that one of the issues is when you have one study with 10 families that data is incredibly important and it's incredibly meaningful and we want to listen to those families, but when making public health policy being

able to synthesis data across multiple studies is crucial, right, thinking about individuals and families in different situations, in different communities, different geographic locations.

I think now that there's a larger effort by the NIH and other entities to do more data sharing of qualitative data, I think there's really great opportunities to think about looking at cross studies at some of these themes and doing thematic analysis in really unique ways, so I absolutely agree.

Committee Discussion

DR. CALONGE: Thanks. Let me open it up to other questions from the Committee, and I see Jennifer's card is up.

DR. KWON: So, I'd like to start with asking, Ned, how should we think about our time to discuss these two very excellent and thought-provoking talks, given that it may give us only 20 minutes for lunch, and that's how long it takes me to get through the line.

DR. CALONGE: We will do our best to do as much discussion and leave as much time for lunch to get

through the line.

DR. KWON: Okay. I think we're overtime. Am I misreading this?

DR. CALONGE: I believe we're okay.

DR. KWON: I apologize. I misread the --

DR. CALONGE: Twenty minutes.

DR. KWON: I'm so eager for lunch, I think. No, but these are both excellent talks, and I guess what I would say is I really like the way you married the qualitative data to the quantitative. And I would just put in a comment that these are consented studies and that the real quantitative data that we should have, and we don't have and may never have can only come for long-term follow--up data collected on children who actually screen positive, so that's- all I would like to say.

DR. GOLDENBERG: I totally agree, and there are a number of studies Beth Turney presented our work on one of the last Committee meetings on following families for a year after receiving uncertain results and with an uncertain prognosis, and one of our goals is to do exactly what you're referring to, which is to follow families more long term to really follow up with families about their experiences and to do so across really over a year of time.

You know a lot of studies are snapshots, right? They are snapshots and just get to the issue of a good day or a bad day, are you talking to people on a good day or a bad day and how does that impact their responses on the survey or their responses on an interview.

One of the reasons why we set up our study the way we did is to give an opportunity to talk to families over time, to hear from them over time, knowing that family stress, for example, increases right before they need to go up for follow-up, right? They might decrease after that appointment and so depending on where you're talking to families in their kind of post-diagnosis clinical process, you're going to get different answers, you're going to get different experiences, and so being able to talk with families over time is really important.

Now, at the same time, it also means respecting their time. Families have a lot on their minds, they have a lot going on, and spending three hours or four hours with you to talk about their experiences means that's time away from their kids, that's time away from their work; also, balancing wanting to hear from those families and respecting their

time is something that we talk a lot about in our work.

DR. ACKERMAN: If I can just jump in to add to what Aaron just said, we also use qualitative methods, interviews, to understand families' responses to surveys, so what Aaron just said about context really matters in terms of interviews and service, so we actually had conducted a survey with the families in our studies around whether they were willing to share their data or not with a national data repository.

And then later, when we interviewed them, we asked them do remember making a decision about data sharing. Quite often, they said no I didn't. And we said, well, if you were to choose now, would you say yes or no, and very often their response was the opposite of what they had answered in the survey, and we realize they were under a lot of duress. They were in a clinic setting. The question was framed in a certain way, so we realized that our survey really didn't get at family's actual preferences, so that's another mixed methods way to help finetune survey questions.

DR. CALONGE: Thanks. Next, I have Jeff.

DR. BROSCO: So, one quick question to your question -- one quick answer, Jennifer -- Jeff Brosco from HRSA -- is that we were hoping that Aaron's and

Sara's presentation this morning would be examples of the kind of evidence that can be useful, not that they're definitively answering questions this morning. And so, this afternoon when we talk about expanding the way we use evidence in decisions for the Committee, these would be examples of the kinds of things that could be done.

DR. KWON: And I guess I just want to respond that people who consent to participate and who participate in these studies are very different from people who don't, and I think that the real harms -- the data on real harms we just don't get because the people who are harmed don't come.

DR. BROSCO: We may have a future presentation from Rachel Grubb. She's done some stuff with the newborn screening, now does more generally to patient experience. I'm going to mess this up, I'm sure, but in her scientific approach to focus groups, instead of getting to consensus and then stopping, it's what are the minority views that come out and then really teasing those out. So, there are some scientific approaches to getting to the typically unheard voices and that may be something for us to consider.

I'm actually going to then turn to Sara, and

my question for you, Sara, you mentioned ethnographic approaches and you're an ethnological expert. Could you say a little bit more about how that might differ from just, say, interviewing someone with a structured interview or what I just mentioned, what Rachel's doing? Could you just tell us a little bit more about the different kinds of ways that interviews might lead to different information?

DR. ACKERMAN: Yes, thanks, that's a quest question. And before I answer that, just to respond to the previous comment, a lot of the families in our study, even though it was a consented study, they didn't even remember they were in a research study. The reason they were in the study is because it was the only way they were going to get access to sequencing because Medicaid did not pay for it. So, just to say that it was a very unusual study, in that sense, that we would ask families and they'd say what research, you know. Even though they went through the consent process, they were so focused on the clinical and personal benefit.

But to get back to your question, Jeff, so I think I would just highlight one particular real difference in ethnographic research versus maybe standard interview, focus group research, and that is

that we were actually able to observe the clinical interactions between families and the clinical team and researchers, and that really helped us to understand that this idea of personal utility isn't something that families -- it's not something they have. It's not something that lives in them. It's something that's actually created in interactions. So, I think -- and the same thing before the pandemic we were actually able to go visit families in their homes when we did research. We asked them would you like to do your interview in our office, in a public place, or at home and they usually said home.

We traveled all over the Bay Area to visit people and we learned a lot about their day-to-day life just by being in their homes. They often showed us where their child slept and they showed us -- you know, a lot of these families were experiencing extreme employment and housing precarity, so we actually got a glimpse into the day-to-day lives of the families that enabled us to understand and contextualize what they were telling us in a way that if we had just talked to them on the phone would never have bene possible. So, there's a lot more to say, but I'll leave it at that for now.

DR. CALONGE: Online we have Ash.

DR. LAL: This is Ash Lal, Committee Member, UCSF. I really appreciate the presentations today. Thank you for your discussion of a very difficult topic. My first observation, just a comment for being a clinician, is that added to the complexity of diagnostic uncertainty is the issue of phenotypic variability and clinical expression of monotypic diseases, so even when we know that there's a definite association, when you're talking to families and trying to describe future course, there're limitations even within that that add to how families perceive the uncertainty around the future of their child.

So, I don't know if that's an additional thing that might need to be added to the counseling of the families receive, not the genetic diagnosis, but the variability of clinical codes in the future.

Sickle Cell is a good example of that, but I'm sure there are many other conditions. But my question is regarding the -- Dr. Goldenberg, the questions that are to be asked what the families' perception of uncertainty in genetic diagnosis, do you think if that the same questions are answered, just as experience, would've bene asked, say, 20 years ago

versus now, would the answers be somewhat different, given the recent advances in the field of genomics as well as precision medicine and the filtering out of some early successes in gene therapy, et cetera, and how that shapes the public's view of genetic diagnoses and prediction.

DR. GOLDENBERG: That's a great question. I'm not sure if they'd be different. I think even 20 years ago when there was still a lot about uncertainty or less information about the kinds of genetic results that families could receive, I still think families' expectations about what they might hear from screening might have been the same.

I do think that back in the late nineties, early 2000s, when studies like this were being done on Alhemizer's Disease genetic testing and Huntington's Disease genetic testing, there tended to be a lot of data that showed pretty significant potential psychosocial harms to families, anxiety to families, and a lot of that hasn't borne out in more recent genetic testing kinds of social science data.

A lot of families have shown a lot more resiliency and a lot more interest, and even when receiving certain results and having some comfort in

uncertainty. Even though we know we're worried about the potential harms of uncertainty, I think even in some of the families that we've been speaking to we've heard that it's less about the harms of uncertainty and more about the resources that families need to address uncertainty and to deal with uncertainty.

And so, maybe families would have thought different 20 years ago than they do now, but I think right now what we're hearing from most of the families in a variety of our studies is less about, well, I don't want uncertain information, or I do want it, but more if I get uncertain information how are you going to help me? What kinds of resources are going to be there to help guide me? How can our family cope together in order to address what that uncertainty looks like, and that includes what you mentioned before, which is that includes when there's phenotypic variability.

So, even if they have a diagnosis and there's phenotypic variability, families want to know what kinds of things can we be doing to look out for particular symptoms or particular things that might reflect that we don't know what an outcome might look like. There's that kind of prognostic uncertainty that we're hearing.

Dr. Ackerman, I know you've thought a lot about these issues too. I don't know if you wanted to weigh in as well.

DR. ACKERMAN: I think you expressed it wonderfully. Yes, I agree about the high tolerance -- in our study population, a high tolerance for uncertainty, but not only a desire for help in managing and obtaining services to help them, but also a real wish that they would be followed by the clinical team.

And so many of the families in our study knew that that was unlikely because they did not have access to clinical genomics care, in general, because of where they lived, because of their insurance, and so it was a sense that they dipped their toe into this elite world of very advanced medicine and then they went out the other side and they didn't know what was going to happen after that and I think that was particularly unfortunate, given a lot of these families day-to-day lives of struggle.

So, I think that's something that I feel is a real unanswered question, not just what researcher's ethical obligations are to study participants after their research ends, but overall, what is our obligation

to families who may not actually have easy access to follow-up care and to help resolve their uncertainty, potentially gain a more concrete answer some day as genomic science advances.

DR. CALONGE: Michele.

DR. CAGGANA: Hi, Michele Caggana, Committee Member. Thanks, Dr. Ackerman and Dr. Goldenberg for those talks, things that we think a lot about in newborn screening, and I agree that these studies are pretty much looking towards the consented population, and it reiterates my question to Dr. Bailey about how you get the full landscape, and I think within the world of newborn screening the word of the decade for us, at least, has been harmonization.

We've been trying to harmonize what we do, how we call results, how we count conditions, what a positive screen is, et cetera, et cetera. And I'm wondering with Screen Plus being a relatively large dataset that's going to get larger, is this a good opportunity to harmonize how these studies are set up to get family perspectives. And like you said, it's important when a question is asked, how it is asked, and I think the answers also depend somewhat on how the information is actually delivered from the health care

system to the family and hooking up to those services.

So, I'm wondering if there's any space to be able to set up some sort of a model that could be then used and put forth into the evidence review based on the types of data that you've both collected.

DR. GOLDENBERG: I mean I think absolutely I think there's an opportunity, just like as we do with clinical data, to think about harmonization, right? There's always this balance between harmonization and context, right, that we always have to be thinking about, which is on one hand we want harmonization and we want precision and we want shared understanding of our definitions, but at the same time you want studies to be able to ask questions the way that they need to for their research questions, right, for their goals or for their particular population or for their communities that they're working with, asking questions.

I use this as an example. Sometimes you're asking questions around trusting government in Flint, Michigan looks very different than even down the road in Ann Arbor, and we need to be able to be thoughtful about that and think about that. AT the same time, I think harmonization across sites is really important and I love the idea of a platform that we work on together

that we share that might help to inform the decision matrix.

And I'll say that I think even though these studies are consented we have found that there's a lot of families who maybe did have bad either experiences or bad outcomes who felt like there's never been an opportunity to talk about, who feel like they haven't been heard or that there haven't been opportunities to talk about their stories as well, right, that only success stories have been heard. And I think these studies do have an opportunity, while I think it is a challenge to bring in those maybe less heard voices.

And I have found in a lot of the work that we do that families who maybe felt like they've been harmed or wronged by programs want to talk about it, even though it maybe difficult or even though it may be a little bit different than the kinds of conversations that we're normally having in this space and I think we can do more of that. I think we can hear from those families a little bit more.

DR. ACKERMAN: So, we conducted a kind of supplemental study where we interviewed community-based service providers, including Special Education teachers, occupational therapists, regional center directors, and

others, and asked them if you encountered a child that just had an etiologic diagnosis with a very rare condition that you didn't know much about, what would you do with that information? They, almost without exception, said, look, if it's a condition that I know maybe that would be helpful, but it's just a really rare, rare disease or condition that it doesn't add much to my functional assessment. You tell me what I can do with it.

So, there really a sense that the knowledge emerging out of advanced genetic technologies is not being integrated or there isn't really any understanding of how to integrate it with existing approaches to assessments in schools and in other community settings, so that seems to be a real need. If we're going to be finding more and more rare variance, more and more rare conditions, how are we going to integrate those different types of knowledge? Because otherwise, we heard from people that, look, that's really interesting, but I don't really see how that's going to change what I've already figured out what this child needs in terms of their developmental trajectory.

DR. CALONGE: Chanika.

DR. PHORNPHUTKUL: Chanika Phornphutkul,

Committee Member. I have a specific question for Dr. Ackerman about the study. So, the consent that was obtained -- what struck me was the family reported that they did not know or didn't recall the yield of this positive outcome, a variant of uncertain significance. Could you just share just who obtained the consent for that because for us who do genetic testing all the time and some sequencing, we have wonderful genetic counselors who focus on making sure that those are some of the key parts of talking to the family. Thank you.

DR. ACKERMAN: Thank you for that question. So, we also had really talented genetic counselors and clinic research coordinators who are obtaining consent. Maybe it would help to explain some of the context, and this is another advance, I think, of ethnography. We were in the room quite often watching this process. So, so many of our families required a medical interpreter to be present, but often this was being done by video interpretation, so there was a device in the room.

Families often brought their affected child and their other children, so the small clinical exam room was packed full of people, the consent was lengthy, there were surveys to be asked. I think it was an overwhelming experience for families and I think they

were really singly focused on, yeah, I want this test. This might help us end our search and let's get through this. So, I think it was conducted in a very rigorous way, but I think the families' priorities and values were not as much focused on the research.

And it's interesting, the clinical research distinction is really blurred in a lot of this emerging genomics research where you have to have families sign both a HIPAA form and a consent form because the research is generating clinical data as well as research data, so it's a lot for families to go through. It's a lot to expect them to remember, especially when there's a language barrier. So, I really think all of those things collided to make this process not always as clear and comprehensible to everyone as we would've liked.

DR. PHORNPHUTKUL: Thank you. And just a quick question, which Dr. Aaron Goldenberg kind of mentioned a little bit. Are there tools to measure resiliencies from social science? Thank you.

DR. GOLDENBERG: Very quickly because I know we're running out of time. There are a number of tools that measure resiliency. There are a number of tools that measure tolerance to uncertainty. There are some

really amazing tools and measures out there. I think they're underutilized. And I can say, speaking as a social scientist that's worked on developing tools, we want people to use our tools. We want people to use the work we're doing, it's just a matter of figuring out the best ways to get them used because these are validated measures that are really fantastic.

DR. CALONGE: Shawn.

DR. MCCANDLESS: Thank you. And I want to echo what others have said. This was a really great presentation this morning, this whole session, so thank you. A quick question, I think, for both Dr. Goldenberg and Dr. Ackerman, related to context and the tolerance for uncertainty.

It seems to me in the data that you both presented that we examine tolerance for uncertainty in sort of an unselected population. We examine tolerance for uncertainty in a group of patients that have already developed tolerance to uncertainty because they've been living with an undiagnosed condition for some period of time.

What we haven't addressed is tolerance for uncertainty in a group of people who actually experienced it when they didn't expect to, which is the

newborn screening situation, right? You have a newborn baby, you get a test done, you have no idea the test was even done, and then somebody comes in and says here's a result. Don't really know what it means. We need to see what's going to happen over the next few years. How do we address the tolerance for uncertainty among that population specifically, or maybe it's been done, and I just missed it.

DR. GOLDENBERG: I'll just quickly say that there haven't been as many studies that have done that. There have been a few, the work of Stefan Timmermans and Mara Buchbinder did that in their book now maybe 10 years ago, the work that Beth and I are working on, and others in the room, some of the work that Don's worked on before has talked to families directly after about what their experience was like getting an uncertain finding.

I think the numbers of families getting uncertain results is going up and that's actually the study that Beth presented, that Dr. - presented at the last meeting is exactly to do that, to capture families, to talk to families right after receiving that information, both quantitatively and qualitatively, and then to follow them over a course of a year, both

quantitatively and quantitatively to sew what that kind of initial shock of getting uncertain information might be and then what that looks like in terms of coping mechanisms in a much longer-term fashion. So, I think that's incredibly value and needed, and I think the same thing- is happening in the larger genomic space.

Dr. Ackerman, I know you know this even better, kind of thinking about talking to people who all of a sudden are placed in a situation of uncertainty.

DR. ACKERMAN: So, I think our prenatal population may be more analogous to the newborn screening scenario and we were fortunate enough to be able to interview some of the families who decided not to undergo prenatal sequencing and it was partly because they just found it overwhelming. It was too much information, it was too much uncertain information, too unclear to them, how they should act on, if the pregnancy was far enough along that termination didn't feel like an option for parents.

They just felt like let's just wait until my child is born and then we can handle this. This is too much right now. But that was actually quite a small minority, so most of the families decided to continue with sequencing and amazing were pretty resilient in

receiving uncertain information. But what was hard for them was being faced with that during what was already a difficult pregnancy and then having questions about future reproductive decisions that really couldn't easily be answered for them at that time and I think they found that very stressful.

So, I don't think there's a simple answer to that question. It probably was harder for that population, I think, than our prenatal families who had years of experience not knowing what caused their child's condition.

DR. CALONGE: Natasha, the last question.

MS. BONHOMME: Hello, Natasha Bonhomme, Genetic Alliance. To the point of uncertainty, I think it's great that we are really starting to focus in on that, but newborn screening doesn't necessarily -- or even genomics doesn't really have an outsized share in terms of uncertainty.

We look at, you have pregnancy, and you go for your typical ultrasound and then, wait, what'd you mean something is there or you have a smooth pregnancy. It was great and wonderful and then all of a sudden, your child is in the NICU. So, I think really as we are hopefully having more of these projects looking at

uncertainty and newborn screening and genomics, we're putting in an even larger context of what uncertainty look like in medicine and when you're going through these different journeys. That wasn't my question. That was a comment.

But two questions or comments for Dr. Ackerman. The population you focused on, you're looking at underserved groups, correct, and then you focused on groups that were through Medicare, Medicaid, is that correct?

DR. ACKERMAN: Well, yes, because California doesn't really have many uninsured children.

MS. BONHOMME: Okay. I actually thought of this first with Dr. Bailey's presentation and then again with yours. So often when we're talking about underserved it seems to be really focused from, first and foremost, an economic lens, and yet, we do know that there are plenty of people who are underserved by our medical systems who have insurance and have all that. Our maternal mortality crisis in this country is a clear viewpoint on that.

I just didn't know if you have any opportunities maybe to compare groups who maybe are not economically disadvantaged, but still medicine is not

necessarily serving them or they're not getting the outcomes, kind of the same thing I'm thinking about as for Dr. Bailey's presentation in terms of family outcomes that underserved can mean a lot of things. It's not just from an economic perspective and just if you had done any work or are thinking of doing any work or any other works, is happening to compare that.

DR. ACKERMAN: Great question, and I have way more to say about that than we have time for, but to just short answer and say, yes, we struggled with NIH's definition of underserved, relying on the medically underserved areas category. Anyway, yes, we really struggled to conceptualize what are we talking about when we say underserved? We think we did not reach the truly underserved because a lot of those families were not referred to our study or could not travel to be in it. And we know this to be true, especially for our prenatal study, because the demographics in the pediatric arm and the prenatal arm were completely different.

So, we actually had much more privileged families enrolling in the prenatal arm. There are a lot of reasons we can talk about why that might have been, but we're very concerned that we certainly don't think

we reached the truly underserved in either arm, but especially the prenatal arm. And these are people who either aren't obtaining good prenatal care. They maybe didn't get a prenatal ultrasound, which is required to be referred to the study, so I think there are a lot of unanswered questions.

And then, I alluded earlier to the capacity of our community hospital partners to actually participate in this kind of testing was really limited. This is where a lot of folks, not just economically underserved, but a lot of folks end up getting care is in community settings. So, there are so many dimensions to what we might mean by underserved and so the ELSI Team stopped using that term. We just started talking about who was in our study population, what their characteristics were, and who we thought we were not actually connecting with and why.

DR. BONHOMME: Great. Thank you.

DR. ACKERMAN: Thank you for that.

MS. BONHOMME: And I'll just email you my other questions. Thank you.

DR. ACKERMAN: Okay, that's great.

DR. CALONGE: Thanks, Natasha. These were great, as people have said, presentations. I think

really added to what we're thinking about in terms of what kind of information can inform us in the harms and benefits area, how we can best capture those and weigh them and hopefully we can move forward. We'll have more discussion this afternoon. With that, I'll turn things over to Leticia, who will discuss lunch.

CDR. MANNING: This is for you, Jennifer. As I stated earlier this morning, the cafe is straight ahead there. The lines shouldn't be that bad today since it's a Monday. There's also a shop where you can pay via credit card, self-pay over there that has sandwiches and chips and drinks of sorts. So, please return here by 1:00 p.m. and we'll start the afternoon off with public comments. Thank you.

Public Comment

DR. CALONGE: During our meetings, these couple of days, we're going to actually have two public comment periods. One today with 10 oral public comments and then comments for tomorrow specifically around Krabbe Disease. We also received four written comments that were shared with the Committee previously as our materials were sent out.

I am asking, that in the order I have focus on my sheet, you come up to this microphone and present to the Committee, and I appreciate you all being here. We're going to start with Maria Kefalas, who is online. Thank you.

MS. KEFALAS: Can you hear me?

DR. CALONGE: Yes.

MS. KEFALAS: Wonderful. Thank you. My name is Maria Kefalas, the cofounder of Cure MLD, an advocacy group that works on behalf of children impacted by metachromatic leukodystrophy.

Two days ago on January 27th, it was the 10-year anniversary of the death of Loie Hammond. She was the only daughter of my dear friends, Matt, and Lauren Hammond. Loie received her MLD diagnosis on Christmas Eve and she succumbed to the disease three years later.

Because the disease attacked Loie's GI system, even with a G-tube, her doctors could not find a way to feed her. That was the main reason for her death. In the final years of her life, the only thing that brought Loie any relief was being held in her parents' arms. MLD parents of untreated children will tell you how the most reliable medicine we have for this

disease is holding our children, letting them hear our hearts beat against their ears and telling them over and over again how much they are loved.

But this year, instead of celebrating Loie's 14th birthday, Loie's parents are counting down the days until FDA approval for OTL 200, a miraculous gene therapy that will ensure that no child suffers as Lowie did. Experts call it one of the most transformational gene therapies ever invented, but for gene therapy to work, MLD needs to be diagnosed at birth since gene therapy cannot reverse the damage to the brain and central nervous system.

In the coming months, the members of this Board will have it in your power to transform MLD into this generation's polio. It is in your power to make MLD a footnote in medical textbooks. There is no doubt the ACHDNC will come to see the RUSP approval for MLD as one of the most singular achievements of newborn screening in the United States during this era of genomic medicine.

We, in the MLD community, are ready to honor the children we have lost. This is Loie's legacy. It is time. Thank you.

DR. CALONGE: Thanks so much, Maria. Thanks

for joining us. Next, I have Paul Orchard, who's also via the Internet. Paul, are you with us?

DR. ORCHARD: I am. Can you hear me?

DR. CALONGE: I can. Thank you so much.

DR. ORCHARD: Excellent. I very much appreciate the opportunity to talk to the group today. I'm Paul Orchard. I'm a pediatrician trained in hematology, oncology, blood marrow transplant, and I wanted to talk also about metachromatic leukodystrophy today.

So, my clinical interest is the use of cellular therapies as treatment for rare, inherited, life-threatening disorders. Over the years in Minnesota, we've transplanted approximately 50 patients with MLD. It's very clear to me that transplantation is not curative. In addition, morbidity and mortality of transplant has been high, 15-20% of the patients die actually going through the procedure, so we clearly need something better.

Fortunately, as Maria had mentioned, an alternative therapy is becoming available, ex vivo lenti gene therapy approach, utilizing the patient's own blood stem cells, introducing a normal copy of the arylsulfatase gene into the cells.

Clinical trials in Europe have been compelling in terms of their data and it's now licensed therapy in the EU, and I'm optimistic that will soon become licensed therapy in the U.S. as well. The FDA is currently considering this and potentially as early as March it may be approved. However, despite the potential for this new therapy, it became clear that it's really the pre-symptomatic patients that are going to benefit from this. The vast majority of the patients that were treated in the clinical trials were second siblings, but diagnosed after a prior sibling was symptomatic. For those symptomatic brothers and sisters, there's really nothing to offer and those patients go onto die.

So, it's fundamentally important to identify these children as soon as possible. The ability to newborn screening has been developed. It's been piloted in a number of placing, including in Germany, where they identified two children that went onto get gene therapy based on newborn screening.

So, in summary, I believe we'll soon a safer, more efficacious therapy for MLD, but if we can't identify these patients in a pre-sympathetic state, they will not have access to it. Development of newborn

screening for MLD is, in my view, critically important and hopefully the addition of the MLD to the RUSP will be something that we could move forward quickly. Thank you very much.

DR. CALONGE: Thanks so much, Paul. And finally, here in the room we have Dean Suhr.

DR. SUHR: Good afternoon and thank you for letting me speak to the Committee and the advisors here. On Paul Orchard's behalf, I'd just like to make a quick disclaimer. We love, Paul. He's a transplanter. He is not affiliated with Orchard Therapeutics, an entirely separate entity, so he brings different information to the table.

I wanted to talk about two things, three things, actually, today. One is the RUSP Roundtable, which I've been mentioning in the last couple of meetings. Assuming that this Committee meets in person in May, we'll be meeting on the Wednesday before it. If you go RUSPrountable.org to learn more and to help contribute to our agenda if you want to participate.

RUPS alignment with MLD is really a reality for us. Every life foundation has been tremendous work bringing nearly a dozen states onboard with RUSP alignment and they have several more. We were also able

to do a RUSP-alignment-like bill with the State of Illinois, so we'll, presuming that you all approve the nomination once it goes through the rigorous process, will have 51% of the babies in the U.S. screening because of RUSP alignment efforts and I think that's something to be very proud of.

But we know that RUSP alignment is not a click your fingers thing. The real work is not in the legislature. It's at the state labs and so we're going to continue our work with the state labs to help them solve their issues and their concerns one by one by one as they implement.

I'm going to skip over much of what's on the rest of this because you heard this from Maria and Paul, Dr. Orchard. The MLD newborn screening pilots continues, both in the U.S. and in Germany. Over 200,000 babies screened, four have been identified, two of them have been onto therapy, but the therapy is not immediately at birth, it's months after birth, so the third baby has not seen that therapy so far.

There are publications that have been made and publications that are being finalized. We froze the data on December 31st, anticipating this March PDUFA FDA approval and, of course, that's a checkbox on the

nomination form. So, we hope to have our nomination, with not only our data, but the FDA approval later on in March.

The only thing I'll say about gene therapy, and those of you who know me well, these words don't come out of my mouth easily, but it's all but curative. I probably won't ever say it's curative, but when given pre-symptomatically, which is newborn screening to identify the patients, these children go onto live normal lives. They run, they walk, they are intellectually and physically competent in comparison to all of our kids and grandkids.

So, we are submitting the RUSP nomination as soon as we can, again, pending the FDA approval and the summary with this data. We've got standards of care, we've got some genotype-phenotype correlation data and information that's in place that will allow for good, positive referrals because we have multiple forms of the disease.

So, we look forward to maybe the next time that we all meet together here that you might be voting or considering to be voting that MLD nomination. Thank you.

DR. CALONGE: Thank you, Dean. We're going

to turn now towards public comments around the Duchenne Muscular Dystrophy. I'm going to start with the Jyoti Bharadwaj.

MS. BHARADWAJ: Hi. Good afternoon, everyone. I'm a parent for a child who's 14-years-old, a boy, his name is Iyan. He has Duchenne Muscular Dystrophy. My son was diagnosed at the age of around three and a half, and this particular disease is a more severe form of muscular dystrophy, which causes progressive degeneration of the muscles. The general progression of this disease is that they lose their ambulation by the time they're eight or nine, restricted to a wheelchair.

They lose the function of their upper body by the time they are in their late teens, around 17, 18. And by the time they reach their early twenties, we unfortunately lose them due to their organ failures and their heart failure,largely.

This disease was found around 50 years back and the work has been ongoing on this since a long time. The current therapies that have come into the market are exon skipping and gene therapy. The gene therapy that has been recently approved is for four- to six-years-old by Sarepta and this is the name of the product. It's

fantastic. I have seen the videos and I have a track with the children and it's great to see kids who are five-year-old and four-year-old who are running, jumping into the pool, and having a good time.

It doesn't sound much to the rest, but when you see your child running for the first time you cry. You stand and cry over there because that's not something that you've ever seen.

Unfortunately, with this disease the progression reflects in a child when they are somewhere around seven years old or six years old. So, getting access to this drug at the right time and as early as possible is extremely critical. Newborn screening is going to probably change the trajectory of this disease completely for the kids. They will have a better quality of life and probably live a normal life. Thank you.

DR. CALONGE: Thank you so much. Next, we have Paul Melmeyer.

MR. MELMEYER: All right. Well, good afternoon, everybody. Thank you for the opportunity to comment on the ongoing review of Duchenne Muscular Dystrophy for consideration for the Recommended Uniform Screening Panel. I am Paul Melmeyer. I'm the Vice

President of Public Policy and Advocacy at the Muscular Dystrophy Association.

MDA is proud to serve the Duchenne, Spinal Muscular Atrophy, and Pompe Communities, along with many other rare, neuromuscular disease communities. And actually, on a note of celebration, SMA has now screened for in all 50 states and D.C., which is an incredible milestone for the SMA community.

First and foremost, we're very grateful for the Committee's ongoing full evidence review of the Duchenne nomination, particularly the work of Dr. Kemper and his team, as the technical expert panel on which MDA is represented. We look forward to continuing to contribute to the evaluation during these quarterly ACHDNC meetings, the TEP, and any other appropriate venue.

The treatment landscape for Duchenne is only becoming more favorable. With about six months of experience now with Elevidys, the Duchenne clinical field now has in dosing four- and five-year-olds with Duchenne. We're very pleased that while access challenges have occurred, to our knowledge, every barrier has actually been surmounted and each eligible boy prescribed Elevidys has successfully obtained the

gene therapy.

Access challenges have included Medicaid agencies, slow-walking the addition of Elevidys to their formularies. Commercial plans have considered Elevidys to be experimental. This is despite, of course, FDA actually approving the product. Self-insured plans have carved out gene therapies in their entirety from their formularies and facilities have borne quite the economic and financial costs by having to purchase the very expensive gene therapy, and then buy-and-build, having to seek reimbursement thereafter.

Nonetheless, through very strong advocacy from the community, from groups like Little Hercules Foundation, from PPMD, from the Muscular Dystrophy Association, each of these barriers have been overcome. In the last several weeks, we convened many of the Duchenne clinical experts, gene therapy prescribers, in particular, to discuss a variety of challenges ongoing within gene therapy development and access.

And what we heard pretty uniformly was certainly a trend in positivity towards the actual prescribing and access of Elevidys, especially compared to when we convened the same group just last year. In addition, we're hearing within our gene therapy support

groups stories similar to the one you just heard about boys running and swimming and jumping for the very first time in their lives and how meaningful that is. Of course, not only to them, but to their families and to their entire support network.

So, with the Agamree soon hitting the market, Deflazacort soon going generic, and the potential expansion of Elevidys labeled beyond four- and five-year-olds potentially later this year, additional therapies advancing through the pipeline, clearly the landscape of treatment for those with Duchenne has never looked brighter. Thank you very much.

DR. CALONGE: Thank you. Next, I would like to turn online, starting with Jennifer Handt.

MS. HANDT: Thank you and good afternoon. My name is Jennifer Handt. My son, Charlie, age six now, was diagnosed with Duchenne Muscular Dystrophy in late 2020 and I then learned that I'm a carrier of his disease mutation. Before diagnosis, we spent the first thousand days of his life wondering why he was developing to slowly, why he wasn't crawling or walking, or pulling himself up.

We asked ourselves constantly was it something to worry about. Our pediatrician told us

repeatedly that it was probably nothing and of course we desperately wanted to believe her. So, during those thousand days, we did things we now regret. We received physical therapy for Charlie through the Connecticut Early Intervention Program. Without a DMD diagnosis, we followed a protocol that pushed baby's unprotected muscles too hard to catch up.

Our baby, who couldn't tell us how difficult or even painful those exercises must've felt. It's heartbreaking to think about that now. During our time, our concerns kept us up at night, but we thought about the extensive newborn screening every baby goes through. Surely, that would've told us if something was seriously wrong. We had no idea what was going on, one of the most common genetic disorders in place was somehow not on that newborn screening for life-threatening disease.

So, beyond the psychological burden of delayed diagnosis, which we absolutely experience, why is this problematic? Right now, medicine is evolving at a rapid clip for DMD. We're at a crucial pivot point with transformative treatments approved and in trials. Yet, even before these advances, high quality care alone has made a difference in DMD outcomes.

Numerous studies have demonstrated that even

in the absence of targeted treatments, coordinated care for DMD alone has resulted in a full 10-year increase in life expectancy. The sooner patients can be diagnosed and begin this care the better, and the sooner we routinely screen babies, the sooner we can truly track how impactful early treatment really is.

For us, once we finally got the diagnosis at age three, we got lucky. We got in with a certified care center quickly and got Charlie on steroids. He turned four at just the right time to qualify for the Phase Three trial of gene therapy now known commercially as Elevidys. We are so grateful for the benefits of Elevidys that we have observed in Charlie so far. Notable improvements in stamina and strength, even the loss of the hallmark Gowers Sign when Charlie gets up off the floor.

But I often wonder what if that timing hadn't worked out so well. It should've not taken three years to get this diagnosis. What if, instead, he had turned six this past August without having had access to Elevidys, which was approved for four- and five-year-olds only? It's really hard to think about that now.

As Elevidys and other treatments become

broadly available, a delay in diagnosis is unnecessary and harmful. It simply does not reflect the current state of science and medicine. There's absolutely no reason in 2024 for parents to play a guessing game or hope for lucky timing with potential treatments or clinical trials. Parents should have the power of knowledge to make the best possible decisions for their children.

Duchenne is the most common pediatric muscular dystrophy. Modern medicine is on its heels and the standard newborn screen is a critical tool we need to beat it. I urge you to add DMD to the recommended screening to let science lead the way and put an end to the guessing game that far too many families continue to play. Thank you.

DR. CALONGE: Thank you, Jennifer. Next, we have Bill Marshall.

DR. MARSHALL: Good afternoon. Okay, I'm a retired pediatrician. I have two grandsons who were recently diagnosed with Duchenne Muscular Dystrophy. My oldest grandson was 32 months old when diagnosed. It came as a shock. I'd had some concerns about motor development but contributed this to normal variation in gait and milestones and perhaps some mild hypertonia.

He'd received regular pediatric care, and aside from a hospitalization for a respiratory virus and had no major illnesses or developmental concerns. He was receiving physical therapy. The first year after diagnosis has been full of life-altered decisions for our family. His physician/scientist mother, his biophysics dad had worked with amazing energy to get him the best medical care and care for his subsequently diagnosed little brother, Leo. Extended family and friends have offered and given physical and emotional and spiritual support. The past year has reinforced my support for newborn screening, even more than clinical data and clinical experience.

As I began my career in the 1970s, I saw that screening could do what traditional medical care did not, make an early diagnosis for treatable disorders. When congenital hypothyroidism, for example, had to be diagnosed clinically, it was often too late. Duchenne's is an analogous situation today. Although the cure is not yet available, treatment with established therapies like steroids, new medications like Exon Skipping drugs and gene replacement therapy and other modalities showing great success.

Beyond medical therapies, earlier

recognition by newborn screening will give families the time and space they need to understand the diagnosis and plan for their new reality: where to live, what home or apartment to live in, whether to have more children are some of the decisions that must be made. As well, early diagnosis will prevent misunderstanding and appropriate treatment and needless investigations.

As the past year has shown our family, these challenges can be overwhelming. Newborn screening will allow all families to begin the steps needed to give their child the best care. I spent my years in pediatrics caring for children from underserved families. Real health equity can only begin when all newborns are screened and then have the prompt, comprehensive medical care, therapy, and peer support that will make for the best outcomes. I've seen too many preventable poor outcomes in other disorders, such as misdiagnosis, lack of medication, interruptions in therapy, that often result from families' difficulties in navigating our very complex health care system.

In summary, newborn screening offers the time families need for understanding a child's illness, the time for life realignments, and the time for early interventions with existing and new therapies. Thank

you very much.

DR. CALONGE: Thank you. Next, we have Aravindhan Veerapandiyan.

DR. VEERAPANDIYAN: Thank you. Good afternoon, everyone. On behalf of the Duchenne condition community, thank you for the opportunity to speak today. So, my name is Dr. Aravindhan Veerapandiyan. I go by Dr. Panda for my patients. I'm an associate professor of Pediatrics at the University of Arkansas for Medical Sciences at Arkansas Children's Hospital.

I run the Comprehensive Neuromuscular Program here, and I also lead our certified Duchenne Care Center, Arkansas Children's Hospital where we follow the 150 children with Duchenne and regular muscular dystrophies. I am also the principal investigator for multiple clinical trials for Duchenne, including the gene therapy trials from Region X, Pfizer, Sarepta, and other downstream therapies, such as CAP 102 and Edgewise, et cetera.

So, Duchenne Muscular Dystrophy currently has seven FDA approved therapies, two Duchenne specific corticoid steroids approved for all children ages two and up, and four mutation specific exon skipping

therapies that are also available to all ages and a gene therapy that was recently approved for children aged four and five years.

Another therapy is under FDA review and more than 20 potential therapies that are in clinical trials. At the typical age of diagnosis, children with Duchenne have muscle damage that is currently irreversible. When muscle tissue is replaced by fat and fibrosis there is no known way to regain it. We have tried multiple alternative mechanisms to improve the age of diagnosis, to reduce the age of diagnosis.

The speakers before were exceptional in terms of age of diagnosis. We are still diagnosing boys with Duchenne at age seven, age eight. Those mechanisms that we have tried are not working. They have not been successful. This is in stark contrast to the success of newborn screening. The benefits of newborn screening for Duchenne Muscular Dystrophy are exponential, enables implementation of the standards of care, which include early intervention services and also considerations for corticoid steroids early on.

Newborn screening means children have access to newly approved therapies, disease modification therapies, including exon skipping and gene transfer

therapy much earlier in the disease process where there is less muscle damage and fibrosis. It also enables them to participate in the clinical trials without concerns of aging out. It gives families the opportunity to learn about the disease and the therapy and clinical trial options.

The newborn screening means that children have the diagnosis prior to starting their school, first learning the evaluations and identification of learning disabilities and other cognitive issues prior to school start so they can have appropriate therapies and support. For the families, it allows timely genetic counseling, identification of carriers who are risk for their own health concerns, earlier development of psychosocial support and time to consider how to best incorporate the diagnosis into the family, which can also affect many downstream choices, such as housing and other support.

We greatly appreciate the opportunity for Duchenne to be discussed again today and I thank you so much.

DR. CALONGE: Thank you. Next, I have Mindy Cameron.

MS. CAMERON: Hi, my name is Mindy Cameron,

and I'm the mother of two sons, including a 22-year-old son named Christopher who lives with Duchenne. Thank you for allowing me a few minutes to talk about my support for including DMD on the federal RUSP.

Newborn screening would make diagnosis, access to specialized care, and early treatment for affected children possible. Without it babies born with DMD will miss the opportunity for the earliest and most effective interventions to substantially slow disease progression, thereby extending their ability to experience a more typical childhood and more inclusive young adult life, and a better chance at survival into adulthood. We know improved health improves lives. This is no different in Duchenne Muscular Dystrophy.

My son did not have the earliest interventions and as he enters his final year of college as undergraduate, he is entirely dependent on caregivers for the most basic daily living and self-care. I can't help but wonder what his current situation would be if he had had the opportunities that are available today, if his disease had progressed more slowly and he had been able to preserve and maintain some of his now lost capabilities.

Would he be able to lift himself out of bed

and into his wheelchair on his own? Would he be able to prepare his own meals? Would he be able to even have a modicum of privacy when he has to use the bathroom or take a shower? Would he be able to take off his coat and hat when he arrives at class on a full day? Would he have more years to enjoy his hobbies, develop relationships, and earn a living as a writer?

But I remind myself that there were no early interventions when Christopher was born. There are now. We have seven approved FDA therapies. Children born with DMD today have a very different journey and I believe they should be given all the tools we have to flourish and thrive in the face of this truly diabolical diagnosis.

In closing, I want to add that newborn screening is also important so that the health of the mother can be assessed, monitored, and treated, if necessary. I did not discover that I was a carrier of Duchenne until my son was nine. By the time I had my first cardiac MRI, when I was in my mid-forties, significant fibrosis consistent with DMD was found and today I take three medications to help preserve the health and function of my own heart. My most recent MRI done just last month showed stability over the past five

years thanks to these interventions, but I wonder if damage could've been diminished if I had started treatment earlier.

We have extensive carrier screening now. We are beginning to gain traction in access to specialized care for carriers. Adding DMD to the RUSP would identify many carrier moms and the relevant family members earlier. Early intervention saves and extends lives and improves the health for everyone affected by this condition. I believe the time is right for the addition of Duchenne Muscular Dystrophy to the Recommended Uniform Screening Panel. Thank you.

DR. CALONGE: Thank you, Mindy. And next, we have Lauren Stanford.

MS. STANFORD: Hi. Good afternoon, everyone. On behalf of Parent Project Muscular Dystrophy, PPMD, and the Duchenne patient community, thank you for the opportunity to speak today. My name is Lauren Stanford and I'm the Director of Advocacy at PPMD. We are grateful for the Committee's continued full evidence review of the Duchenne nomination package. We look forward to continuing to help the Committee in any way possible as they continue this review.

Duchenne currently has multiple approved

therapies and is in the middle of dramatic changes in treatment paradigms with more than 20 additional potential therapies in development. The approved gene therapy, Elevidys, is currently being dosed in four to five--year---olds and there is hope for an expanded label later this year.

The approved treatments are effective, but they are also long-term. They require long-term treatment and then provide long--term benefits. Traditional outcome benefits are unlikely to be visible in early childhood for Duchenne, because the typical development of disease course. It would be so beneficial to find a cohort of voice- diagnosed at or near birth and then follow them for five or 10 or really 15 years, but that has not been possible in the past.

Newborn screening for Duchenne would allow for those living with Duchenne to receive treatment earlier and then we'd be able to collect this data. Newborn screening saves lives, but current treatments for Duchenne are not cures. However, the available treatments do delay or slow muscle damage and because they are slow in delaying muscle damage, we know they are going to get benefit from newborn screening.

As far as how much benefit, it is going to

take years to really know what that looks like. We've gotten survival to the late twenties with our SOC treatment. Maybe we'll get another five years of walking or ten years of incredibly important upper extremity use, or another 20 years of life, and every single one of those would make Duchenne newborn screening worth it. We hope that the Committee will see the value of adding Duchenne to the RUSP. Thank you.

DR. CALONGE: Thank you so much. This ends our first public comment period. I want to thank everyone who came to the Committee and shared your lived experiences, your families' stories, and your expertise. It's an important part of federal advisory committees, something we value, and something we couldn't do our work well without that input, so again, my appreciation for everything that you do, and you've done for the Committee and newborn screening moving forward.

Duchenne Muscular Dystrophy Evidence-Based Review: Phase 2 Update

DR. CALONGE: As you all know, in August of last year we voted DMD to go forward for a full evidence review and this afternoon and next actually, we're going

to have a presentation from Dr. Alex Kemper for the Phase II part of the study. Dr. Kemper is the Division Chief of Primary Care Pediatrics at Patient- wide Children's Hospital and Professor of Pediatrics at the Ohio State University College of Medicine. His research focuses on the delivery of preventive care services, including newborn screening, and since 2013, Dr. Kemper has served as the deputy editor of Pediatrics. So, we're so thrilled to have him here to present Phase II updated.

DR. KEMPER: Thank you very much, Dr. Calonge, and it's a pleasure to be able to give an update with where we are with our work. With this update, the primary goal is just to let you know where we are with evidence review. We're not going to drill in too deep to the evidence today because we want to make sure that when we come back at the next meeting, we can provide a full and balanced view about what is known instead of drilling into just small areas.

Of course, I'd like to thank everybody who is a member of our evidence review group, as well as Dr. Dorley and Dr. Phornphutkul, who serve as the liaisons for the Advisory Committee to our work. But perhaps, most importantly, I want to thank our Technical Expert

Panel members who really helped guide us through the evidence and make sure that we understand things appropriately. We couldn't do our work without their involvement.

So, now for a quick update on our activities, we've had the first Technical Expert Panel callback in October and we're planning for a second call in February or March to go over where we are with the evidence review and make sure that we're understanding things appropriately. The literature review is in progress. As you might expect about DMD, there's a much larger body of literature than there is for some of the other rare diseases that we've looked at with in excess of 7,000 articles that we are going through.

We've begun the process of the Public Health System Impact Assessment. There was a webinar that was held on January 17th to review the salient features of Duchenne Muscular Dystrophy newborn screening with representatives from the state newborn screening programs. There's a survey that is open and it'll stay open for about another month, and we've just begun scheduling key informant interviews.

Next, we're going to be also -- and this will begin with the next Technical Expert Panel call

discussing the decision analytic modeling that is asking ourselves what might happen if you were to screen all 3.65 million newborns in the country each year for DMD. And then, of course, our plan at the next meeting of the Advisory Committee to have the final evidence review.

So, in terms of newborn screening activity, I do want to let you know that there are two states with legislation for DMD newborn screening, and in addition, in Minnesota, Arizona, and Illinois there's a lot of activity that will likely lead to DMD newborn screening in the near term.

I want to talk a little bit about the treatment. We had heard previously about the FDA-approved therapies. This is a list of the exon skipping drugs, which received accelerated approval from the FDA. When you look at what lead to the approval, in general, it's mean change in dystrophin, not necessarily a functional clinical outcome, but this biomarker of mean change in dystrophin you can see the years that these drugs were approved, ranging from 2016 to 2021. The particular exon that's skipped, a summary of the pivotal studies that were done and then clinical outcomes where they have been reported as part of the package leading to this FDA accelerated approval.

Again, I just want to highlight that most of the focus has been on the mean change in dystrophin, so as you'll hear about in a little bit, one of the things that's really important for us to be able to look at and inform the Advisory Committee is what we know about the relationship between biomarkers and functional outcomes.

Gene therapy, it's my goal that by the time I come back to present to the Advisory Committee that I can pronounce the generic name for gene therapy, but don't hold me to that. The gene therapy received FDA approval for children ages four and five. You heard a little bit about this from the public comment a little bit ago, and it's really critically important to think about the approval has been made because the average age of diagnosis would preclude gene therapy for many children, and based on registry data it's clear that minoritized children have a longer average time to diagnosis, which could lead to important disparities in access to therapy.

There have been three main studies of gene therapy and interpreting some of these studies is difficult. There was a problem in one of the studies with the dosaging error that reduced the effective sample size. There is listed here trends at 48 weeks

among subjects four- and five-year-olds towards improvement in the North Star Ambulatory Assessment, which is a standardized measure, but again, it's complicated because of trends in the NSAA over time and exactly where things were looked at. And again, these are small studies that were underpowered for some of the things we might want to look at in terms of functional outcome.

The other mean, medical therapy is Glucocorticoids, there's deflazacort. Again, you heard about that a few minutes ago, which was FDA-approved in 2017. There was a randomized double-blind placebo-controlled trial for 12 weeks that had an extension and was associated with improved muscle strength compared to placebo in children who are five to 15 years of age. And there was also another randomized, double-blinded placebo-controlled trial that went into 140 weeks of treatments for loss of ambulation, again, with older children, six to 12 years of age that showed a difference in the loss of ambulation.

And then, in addition to deflazacort, prednisone can be used as a Glucocorticoid for treatments in children with DMD. It's typically started before the plateau phase, which is around four to five

years of age. So, one of the things that you can see is some of these gene therapies, Glucocorticoid therapy doesn't happen in infancy, but really at the ripe old age of four and five and so forth.

So, I do want to talk a little bit about areas of focus for the review. I talked a little bit ago about the link between the amount of dystrophin and functional outcomes and also the treatment benefits from presymptomatic identification. So, what are the benefits to the children identified in early infancy, especially when some of the medication therapies wouldn't be provided until later?

And that brings up the issue of non-pharmacologic interventions. So, in terms of the benefits to the individual and the family, again, we're still reviewing articles from the search. The Advisory Committee at one of the earlier meetings asked about studies of siblings where you can compare outcomes from an older sibling who might have been diagnosed through usual clinical care to a younger sibling who was picked up because of the diagnosis in the older sibling. That's been an important piece of the evidence for some of the other reviews that we've done.

We haven't identified any peer-reviewed

published sibling studies, but we did find three meeting abstracts that provide some information. But we're contacting the authors to get additional information and I'd like to hold off until we have a better sense, you know, given how brief abstracts are. There are some reasons that have been put forth to us about why we don't see these sibling studies related to, in some cases, families decide not to have another sibling once a child is diagnosed in a family and then there are also complications around genotype-phenotype correlation even between siblings.

In any case, we're still looking for this. And again, through the other articles that we're going through really trying to best identify the benefits to the individual and the family.

So, in terms of next steps, we're focusing on the impact of presymptomatic identification compared with usual clinical identification, looking specifically at individual and family benefit, inequities in diagnosis and treatment, and then understanding the relationship between biomarkers and patient-centered outcomes. We're also trying to better understand how screening might be implemented within newborn screening programs.

So, as I talked about in my last presentation, CK-MM is the standard first tier screen, but there are different ways of using it, right? So, you could do one CK-MM and if that's elevated move onto molecular analysis or you could repeat and so there's different ways of doing that. And then, once it's decided that the child would benefit from gene sequencing there are questions about who's going to do that. Is that done through the newborn screening lab as part of the work that the newborn screening lab does or is that part of a diagnostic referral? Again, that makes differences in terms of thinking about how this would be operationalized if it were to be recommended.

Again, we're focusing on understanding perspectives from the newborn screening programs as part of the PHSI survey that we do, and then modeling expected outcomes for screening the 3.65 million babies that are born each year. So again, this is a very high-level summary of where we are. I'm happy to answer any questions or take additional direction from the Advisory Committee.

Committee Discussion

DR. CALONGE: Thank you, Alex. Let me open

the meeting to questions or comments, first with the Committee Members. Jeff.

DR. BROSCO: Jeff Brosco, HRSA. Thanks Alex. Could you say a word or two about the role of the TEP and how they help in this? As I understand it, they are folks that you think have the most expertise in this and part of it is that they can help guide you to literature that may not show up in the 7,000 or is easy to miss.

DR. KEMPER: I think you summarized it exactly right. So, there are 7,000 articles. We want to make sure that we're understanding this correctly. The other thing is the field has evolved, right, over many years and so helping us understand the lay of the land is critical. Again, we don't want to miss anything that's really important and so we do the best we can in terms of sharing our work product with the Technical Expert Panel. Beforehand, we're happy to talk to advocates to best understand. I mean, at the end of the day, our work is well defined by the manual of procedures that's been approved by the Advisory Committee in terms of the level of evidence and how we go about doing our work, but we wouldn't be able to do it without that kind of close partnership.

DR. CALONGE: Alex, maybe you want to wait until you understand it more, but you talked a little bit about the elements of the improvement assessment scale you're using.

DR. KEMPER: For the children?

DR. CALONGE: For the children.

DR. KEMPER: The standard one that's used is the North Star Ambulatory Assessments. I'm looking at Dr. Ream out there. He knows much more about it than I actually do, but that's the standard one that's used within the world of Duchenne Muscular Dystrophy, but there are other measures too of outcomes in terms of talking about tying to loss of ambulation, need for additional pulmonary breathing support, and stuff like that. But if you look across the studies that have gone to the FDA, it's the North Start Ambulatory Assessment that's generally used. And if you want particular details, then I'll plead the fifth and wait until the next meeting to share all of the elements that are in it.

DR. CALONGE: Fair enough. The question is, are there elements that might flatten the curve of improvement more than another, when you average them together, so I'll wait for that.

DR. KEMPER: We'll have the answer for you.

DR. CALONGE: Scott.

DR. SHONE: Scott Shone, org rep from ASTHO. I guess, Alex, can you help me understand the not reported clinical outcomes for these and what does that mean in terms of how it got through approval and juxtapose that with where do you think you're going to find the data to help drive -- I thought I heard you say, so correct me if I'm wrong. There's not a lot published and there wasn't a lot in FDA, so where does that data come from for Phase III.

DR. KEMP: There's a lot that's published on DMD and on the use of the drugs and those kinds of things. What was reported to the FDA is, by and large, these biochemical markers of change and it's the patient-centered outcomes that I think usually carry the most weight, which we want to be able to provide. The other thing is that we're really focused, not on whether or not the drugs work, but is there an incremental benefit for the children that are detected -presymptomatically through screening or however else they might be identified- versus usual clinical care.

And I should have mentioned this, but I

didn't mention it in my talk, is that let's say something like gene therapy, right, you're not eligible for it until four years, although the FDA may lower that, but let's just say you're not eligible for it for four years. Does presymptomatic identification mean that by the time you're four years old and eligible for therapy that you're clinically better and more likely to have a better outcome?

So, it becomes very nuanced. It's not just a matter of looking at the direct benefit in terms of patient-centered outcomes, but also comparing the differences in patient-centered outcomes between early identification and later identification and those are the kinds of things that we're- really focused on.

At the end of the day, most of the information that I may provide when I come back, may be around biomarkers and those kinds of things, but again, I'm hopeful that we're going to find more articles around or evidence around patient-centered outcomes. Does that answer your question? -I know I kind of went off on a tangent.

DR. SHONE: Well, no, you clarified that the challenges seem to me to be linking the biomarker outcomes to the patient outcomes and that’s where the

potential gap or yet to be identified.

DR. KEMPER: Yes.

DR. SHONE: All right, thanks.

DR. CALONGE: Online we have Melissa.

DR. PARISI: Hi, Melissa Parisi, from NIH. And I just had a question for you, Alex, kind of reflecting some of the comments made during the open comment sections. Are there any data that you're aware of that actually show the prevention of damage or harm that can occur by earlier diagnosis, and I'm referring to some of the comments related to ensuring that kids with the diagnosis of Duchenne Muscular Dystrophy get appropriate physical therapy, access to steroids, and other interventions that will help preserve muscle strength and muscle function as long as possible.

DR. KEMPER: That's really one of the key questions that we're looking into. I'm afraid to give you an answer before we're all done in terms of potentially biasing the Advisory Committee in terms of giving a yes or no answer, those kinds of things. What I can tell you is that we're finding some evidence that would support that, but we want to follow it with authors, like the sibling studies that I mentioned before, to be able to get to that.

So, what I can tell you is that there is some evidence out there about it in terms of the magnitude of difference. I'd rather just not say until we've gone through it in greater detail, but that's the key question that we're focused on. I know that's unsatisfying, but I just don't want to give a wrong answer.

DR. PARISI: No, I appreciate it. You're still in the midst of the review, so I appreciate your response.

DR. CALONGE: Robert.

DR. OSTRANDER: Robert Ostrander, American Academy of Family Physicians. I want to jump back to your comment about one of the things we need to do is to sort out whether it makes sense to do newborn screening if we're not going to start treatment until four. And this takes us back to a discussion that I think we've had in the past about distinguishing between presymptomatic treatment and treatments that are driven by the usual approach to care because diagnosing someone through newborn screening, which reduces health disparities in addition, allows one to start a treatment that is indicated at age four, when perhaps the time to diagnose is with the usual clinical care might be six.

So, I'd be interested as you come back next time distinguishing between those two concepts, usual clinical care and presymptomatic care.

DR. KEMPER: You probably have another little rejoinder, was that the end of the question, because I just want to jump in real fast. So, there's really a couple of different issues you're talking about. One is if you identify somebody pre-symptomatically, by the time they become eligible for a particular intervention, are they doing better, right, less muscle damage and those kinds of things. But I think we need to be very careful, especially in the context to Duchenne Muscular Dystrophy to not think intervention equals medicine because there are lots of other interventions that can happen even before, say, four years and you get your gene therapy.

DR. OSTRANDER: I didn't want to beat that horse because I'm always the guy that ends up, stands up, and says that.

DR. KEMPER: I k now. I felt honored to be able to say that for you.

DR. OSTRANDER: I almost in my question said even with narrow diseased-focused medical therapies there may be advantage to diagnosis years before the

onset of treatment, but still where people would be delay because of the usual clinical care the diagnosis might not be made for a couple more years. Thank you. I guess I'd say that. I didn't beat that horse again to avoid consternation from all my friends here.

DR. CALONGE: Jennifer.

DR. KWON: I thought the questions that were raised were very important and it sounds like you've heard them as well and that hopefully at the next presentation you'll be able to connect some of these dots. But I just wanted to make sure that I understood Scott's question. Were you referring to the slide of exon skipping treatments and the lack of clinical outcomes and how that tied in with the biologic markers? And I think that in the Duchenne community, but just in the pediatric treatment community, as you probably know, there was some controversy about FDA approval for those treatments. And so, again, I think that's one of the things that we hope to hear more about.

But in response to Melissa's question, I think it was really about early treatment, how many of these drugs are being used earlier than four years, than three years? How many of them are being used in infants? Some of them are, and yet, I don't know of a

lot of publications, so I think that would be a very interesting thing for the TEP to bring forward to help you review if it ends up being gray literature and for us to hear about.

DR. CALONGE: Thanks, Jennifer. I think that ends our session on Phase II, and thank you, Alex.

(Applause)

DR. CALONGE: So, as I said before, during the last year we've done a significant of work in looking at our processes across the Committee's work. Back in May, Dr. Kemper provided a background on the current decision matrix pool. We had a good conversation at that time about updating the process and actually having it more closely match what we've been doing for the last several years and the last few conditions that we voted on recommendations for.

During the November meeting, we were in consensus with the proposed updates, which we can provide, they are on the website at this time, but we also recommended to convene a group of experts to discuss the Public Health Impact Assessment portion of the decision matrix tool. And today, I'm going to be sharing a proposal for the Impact Assessment that we've discussed with this group.

So, just as a reminder, the basic concept is the letter grade, which refers to the magnitude of net benefit and the certainty of net benefit is a separate consideration than Public Health impact Assessment. They are part of the same matrix, that is, the information from the assessment needs to inform and be considered by the Committee in making its recommendation. But we felt that building it in so that you were a B2 or a B1 wasn't quite in the spirit of how other evidence to decision frameworks work, which are almost always based on the evidence of benefit and harm and then the certainty around that evidence.

Yet, the assessment of public health impact is both a statutory requirement for the Committee and an important process for going forward in making decisions.

So, what I'd like to do is present some slides that I believe captured what we talked about in this Public Health Impact Assessment Group. Now, these are draft. They're not set in stone. They're more for discussion. Those who attended the meeting tell me whether or not I captured it right in drafting these, with Jeff and Leticia's help, and I look forward to the discussion.

The way we thought about doing this is in

two phases. And the first phase would be let's learn from those who've already done it because there's a rich knowledge base in actually running a pilot program. And in terms of what we need to ask or assess in the other states should be based on what we've learned from those pilot states.

So, this is a Phase I approach. There's a set of questions around what it would take for you to do this? And so, the questions start with core testing, which, for the sake of the discussion, I said this would include confirmatory testing as part of the process. So, we thought, well, what did it take? Did you need new equipment? For some of the conditions, just turning on a segment of the signal from tandem mass spec or adding a new algorithm is something you could build onto the equipment you now have.

If you already have sequencing equipment, then even adding a genomic confirmatory test may only take turning something on, but for other states there could be a cost of obtaining new equipment. And if that was required for the pilot test, what was the estimated cost, time to install and set up, and did you actually need to build out new space? So, I know these sound perhaps mundane, but they're critical parts of a newborn

screening laboratory thinking about how can I implement this and what is it going to take.

I look at these and my experience with the Colorado State Newborn Screening Program is we had to do all of these when we added a new condition. So, thinking about what did it take in that, and then did you need more staff? So, how many more staff did you need, was it like incremental staff, a part of a FTE or laboratory scientists or more?

And given that, how long did it take for you to hire that person and it's through whatever system your state laboratory needs to go through in order to add personnel, what was the time. And then, finally, was there different expertise you needed?

So, those of us who hire people -- I know there are lot of them in the room -- these are all things that you have to think about when you're adding new FTE, especially for a new process. So, another concept, okay, we're adding a new test. What from the personnel standpoint did I have to add? And then finally, there's some really important logistic issues that we've heard about in talking to newborn screening laboratories and programs in the state, like did this require new authorizing legislations?

We've heard there are a number of states that require adding the topic as soon as it's approved on the RUSP, but did you need new authorizing legislation, did you need new appropriations, funds and/or FTE? In Colorado, those are two separate decisions. I don't know why, but they're two separate decisions.

And then, if you did have to add these things, what was the time to acquire authorization and/or appropriation? So, we're trying to get a concept of cost and time.

So, then we moved onto questions around follow-up. Again, on diagnostic confirmation, what was the estimated cost and what was the estimated time to develop? In terms of first-year treatment, what was the estimated cost? -And again, now working with the health care delivery system and the experts who are providing the care, what did it cost to get this set up for the first year and how long did it take you to develop it?

Did you need new funding required for follow-up? And if yes, how much more and how long did it take for you to develop that funding?

So, the idea is now we have a picture of the impact on states that were successful in doing it, so in

essence, they've actually said it's feasible, right, because they've done it, and this is what it took to get there.

So, the second phase will be to reach out to states who are not pilot states, reach out to states who might be quick to implement, might take a longer period of time, might take a long time to implement so we have a good picture of the different stages of readiness for implementation.

Here the questions are different. Based on the pilot information, which we would summarize for the survey, if the condition is added to the RUSP could you implement testing within two years? That's a nice dichotomous answer. You notice we didn't draft "well maybe" or "it depends." We just could you. What resources or additional support would you need to do this, external support for startup from our friends at HRSA or potentially CDC? What about regionalization agreements or other things to make it possible for other resources?

And then, again, specifically, if we added this condition to the RUSP, are you planning to start working on implementation within the next two years, yes, or no? So, how this would come into the decision

matrix would be answers to these questions: What's the estimated time and cost to implement testing that we obtain from the pilot states, what proportion of respondent states can implement in two years, what proportion would start implementation in two years, and what proportion of states would require additional external support to implement, when the survey process would be begin after a nominated condition is accepted for review by the Nomination and Prioritization Workgroup?

So, we want to time it in such a way that the assessment wouldn't slow down implementation or let me say it differently. Wouldn't slow down the process to vote on recommending the condition to the RUSP. And then, again, the Phase II survey should include states that are likely to move quickly towards implementation and those for whom implementation will be challenging.

I would like to -- again, recognizing this is draft, that it's the first time that I think even the members of the Ad Hoc Working Group have seen it in this format. I'd like to open up the floor for discussion. And if it's okay, I'll sit back down for that. Does anybody, other than Scott, have the first question? Just kidding. Scott.

DR. SHONE: I was just looking at the Committee to make sure I didn't overstep the organizational rep. So, Scott Shone, ASTHO. So, first I want to make a comment that the follow-up slide also needs questions about staffing. So, you have staffing on lab, but particularly, depending upon how the test performs, what additional second, third tier tests are needed to be tracked and results our follow-up colleagues need to assure that there's staffing as well, so I would strongly suggest that that be considered in addition to just costs. There's actually a human power issue on this follow-up side.

But my question is where did two years come from? Is that based solely on the tidal wave of RUSP alignment legislation that's going along because the two years -- I think that this Committee has had several presentations. NewSTEPs has tracked implementation timelines for the last several years and I think there's a good level of quantitative data to show, in many instances, how long things are taking and why. And whether it's all the steps you talked about, legislation, fee increase, hiring, contracting, all those things that we've talked about at this Committee beyond just actually validating a test in a lab and

establishing a follow-up protocol and I think the data has routinely showed that it's longer than two, so I just wanted to know why two was chosen for this.

DR. CALONGE: It was chosen to have this discussion. There was another vote for three years and it was moved to two. I don't know what the right number should be, but I think what we do want to do is to share with the advocacy and family communities that we think moving forward quickly is important.

DR. SHONE: I'm not saying that I object to two years. I was saying North Carolina we have three years and there are tests that implement and can implement in a year or so and there's tests that do take longer for a variety of reasons, so I wasn't passing judgment on two years. I was just trying to understand why that was part of that.

DR. CALONGE: And I didn't hear it. I just told you we had to pick a time and that was the one we chose. Thanks. Other comments, Scott, before I move on?

DR. BROSCO: Can I ask a follow-up?

DR. CALONGE: Yes.

DR. BROSCO: And you're asking the newborn screening people here. It's always this feasibility

time thing tradeoff. The reason why we think it's whether it's two years or three years was the right one was so important is that if I say to you how long will it take to devise a novel vaccine based on mRNA technology for a virus we've never seen before and deliver it to hundreds of millions of people, you'd say forever, unless it took the entire nation's resources to do it and it was done in nine months or whatever.

So, part of it is how much resources would it take to do in two years versus a year versus three years. And so, my question for you is, is it really a tradeoff between resources? I mean, if you had enough resources, you could do it in two years, or is it, no matter how much you had it would still take two.

DR. SHONE: Obviously, as we've talked about and has been talked about even today that there are state-to-state differences in how this is answered.

I'm going to answer from North Carolina's perspective. A fee increase will take no less than nine months, right? So, that's automatic in terms of how long the process would take on that aspect alone, not to mention the month-to-month process to establish positions that can't start until you have fees, the contracting process, all of that. So, I think that what

I reacted to was one of the questions was what would it take to do it and I didn't know if it meant what would it take to do it in two years or what would it take to just get it implemented and I want timeline. Because in a sense where a procurement process takes nine months, I have no jurisdiction over that, and most public health labs and -followup- managers have no authority over how long a state procurement process takes.

And I agree, if this was purely left up to laboratories and follow-up program through the newborn screening programs that are comprised of laboratories and follow-up staff, that the process likely wouldn't take two years because everybody is committed to doing it as fast as possible. And I think that when you talk about that, that is the case, but I think that the problem is broader. And it's not just a newborn screening issue. It's a public health issue.

But if you have billions of dollars like we did for the vaccine to pour into adding new conditions, I think that the public health system would welcome that and expedite adding conditions for newborn screening.

DR. CALONGE: Fair enough. Thanks, Scott. Susan.

DR. TANKSLEY: Hi, Susan Tanksley,

Association of Public Health Laboratories. So, I'm not sure where all my questions are, but I'll start with an easy one. So, for Phase II, so this is after you have information from the pilot states, the survey states, then my assumption at that point was all the other states, but then in your closing slide it alluded to a smaller number, which includes states that are likely to move quickly towards implementation and those for whom implementation will be challenging. And so, I'm wondering what your thoughts are as to that number that you would look at in Phase II or is that all states?

DR. CALONGE: Great question. It's a conversation we had at the working group and the idea is that we won't necessarily have to do all states, but we'd need a representative sample and we thought we wanted to make sure to include states that say, yeah, bring it on. I mean there will be states who contract out all of their newborn screening, so as soon as the signal can be turned on at Perkin Elmer or Mayo or wherever the samples go, they could start doing it.

And then there will be states that have, I would say, more resource limitations than other states for whom adding almost any condition is going to be a challenge. And the idea is to make sure that we have a

representative sample of everything from one to the other. We could do all states and it would be a question back after the discussion to the working group. We just think it could be more efficient if we did representative sampling, but then we might miss somebody who's different from other states.

DR. TANKSLEY: Would there be a survey, or would that be based on history as far as how long it's taken to implement conditions? It's like do you base that on data or is there another method for that?

DR. CALONGE: No, I think we were thinking about like personal knowledge and experience. But on the other hand, it could be all states. It's just that we know that all states don't respond to the survey. And the other issue is that we want to make sure that when the survey went out that it did include states representative across the spectrum of readiness to implement.

DR. TANKSLEY: Okay, one more follow-up question. So, on the three questions that would be asked based on the pilot information. So, A, was if it was added to the RUSP, could you implement testing within two years, which you've already discussed. And the "C" one is if the condition is added to the RUSP,

are you planning to start working on implementation within the next two years. So, is that to like to measure a willingness or another step I the process or is that just like a process. It's like, okay, it will take you more than two years, how far can you get?

DR. CALONGE: You got it. So, the idea is, if we added this, would you start working on it right away, would you work on it after you've worked your way through other conditions that were added before this? So, kind of getting an idea of when the two years might start. And I'm trying to think of the best way to answer that. Again, remember these are draft, I appreciate that, and thinking about what's the information that would be most useful to the Committee to consider in terms of what's the public health impact of saying we're going to recommend this today.

DR. TANKSLEY: One comment and then I'll stop is that when you do ask these questions you do need to allow for additional comments.

DR. CALONGE: Yes.

DR. TANKSLEY: Thank you.

DR. CALONGE: In fact, it's the additional comments where all the really important information is, so I appreciate that. Debra, I'm going to come back. I

just saw a Committee Member. Shawn?

DR. MCANDLESS: Thanks. Shawn McCandless, Committee Member. So, how do you anticipate incorporating this information into the decision matrix? That's what's not clear to me.

DR. CALONGE: It's really just so simple. The answers to the questions will be on the matrix slide, so they will be yours to consider or ours to consider as we think about the vote. So, they're not going to fit into making gradations among the As and Bs, but what they will do is provide information for the Committee to think about as they contemplate their vote to add or not add. Okay, first I have Michele and then Carla.

DR. CAGGANA: Hi, Michele Caggana, Committee Member. I think one of the other things behind "C" on that slide about the implementation, also can help separate the states that do not have the RUSP alignment legislation, per se, so it gives for states that don't have that extra-legal pressure to implement within 18 months, two years, three years. We can also get some information on those, outside of that.

DR. CALONGE: Great comment. Thank you. Carla.

DR. CUTHBERT: Carla Cuthbert, CDC. So, this is a follow-up to what Shawn was just saying about how this is going to be used. So, if the state can't bring this up in two years, maybe they can bring it up in five and, generally, the consensus is that many of the states maybe can bring this up in between three to seven years. It seems to me that this is just to temper our expectation as to when this can actually be done, but if it has a strong benefit and all of those other things, we're likely not to say no to it. It's just that it's not going to happen right away. It'll just take a lot more time, right?

DR. CALONGE: Jeff.

DR. BROSCO: Jeff Brosco, HRSA. So, this is, again, a question for the state lab folks. I think, Carla, that's a really good point and so part of it maybe I'm a state health department and this was just put on the RUSP, but, man, this is going to take five years on average. Is that helpful to state labs and departments of health to be able to say, yes, we're going to added to RUSP, but look, this is going to take a while, recognize that, but it doesn't stop us, as a Committee, from voting for something on the RUSP because of what you said, it's highly valuable. But it does

temper expectations and make it easier at the state level, but maybe that's a hypothesis, not knowledge. I don't know what you guys think.

DR. CALONGE: Well, I think the other thing, Carla, was we actually hope that we could have information on what it would take, so the cost and time implementation, the FTE, the space, the relationships with clinical providers to do diagnostic and follow-up care. I think thinking about the impact on the entire system is useful for the Committee and then hopefully useful to our federal partners in thinking about might they have resources to bring to bear, especially for a condition that the Committee feels overwhelmingly positive about the impact of implementing this. So, I'm not asking you for money yet, but we will be. Debra.

DR. FREEDENBERG: Thank you. So, I just wanted to clarify and comment a little bit about the inclusion of the clinic centers' input into this. I think that traditionally when we survey clinical centers input that's the most difficult information to receive because (A) either they're not invested or (B) they don't have the answers and that they don't have the time.

And I know that as new conditions have come

on, we've sent them out to the clinical centers treating that particular type of conditions and even with a lot of, let's say browbeating to get results back, that's always been very difficult, so I think we need to think a little broader about strengthening those relationships as well as what it is that you're actually asking the clinical centers to be doing, what their role would be, whether it would just be treatment or confirmatory or whatever it is, I think we just need to think pretty discretely about that.

DR. CALONGE: I appreciate that. I wonder if you have any suggestions to strengthen relationships. So, what I do in Colorado is I call Shawn up and I say who do I need to talk to over there at Children's and he always comes up with a name. Almost all of them will talk to me, but that's Colorado and I just don't have a sense for, are there other strategies that we should be pursuing and thinking about completion of the assessment, so that it's reflective of the challenges of putting this together.

DR. FREEDENBERG: I think you put your finger on this because it's really the personal relationships that really make the difference in getting those responses back and that you call people, you've

known them, you've worked with them, and you try and get those responses back. But even with that, it's like pulling teeth to try and get responses back. And then sometimes you get responses back and you get two back and one says (A) and the other is diametrically opposed and says (B) and then what's your recommendation at that point? You've just neutralized everything.

DR. CALONGE: Especially when they're from the same institution.

DR. FREEDENBERG: Exactly.

DR. CALONGE: Yes. Well, those are good comments. I think thinking about how to do the assessment and the strategies for collecting information is a really good point. I'm sorry, Jelili, I don't know how the survey is done now, or Susan or Scott, but I do know that there's a strategy of scheduling an interview. It's easier to answer the phone than it is to find the time to fill out a form that's not talking to you. So, just thinking about other strategies to complete the information is something we'll look at.

Now, I've got questions online, so I'm going to start with Ash.

DR. LAL: Ash Lal, Committee Member. And I just wanted to, if we go back to what Shawn had

mentioned a few minutes back, I think we were moved to separate out the feasibility of public health site cost, the newborn screening, new conditions from the net benefit and the reason for that, and I think it might be in your next presentation too, is that how should the Committee view information when the decision is primarily based on net benefit on the feasibility of implementation.

If that information is provided at the time that you vote a new condition, would we have to set up some kind of guidelines on how the information should actually be used and how you think it potentially would impact the vote.

DR. CALONGE: I think it is something the Committee could consider. And again, getting to the condition where the Committee feels strongly that it should be voted to be added to the RUSP, but there are some public health impact challenges that thinking about what the Committee can do in working with federal partners or others to say we understand that and we want to figure out ways to ease implementation in the states over time.

And the Committee could do what I think we really want to do, which is expand our purview over more

than just voting on conditions under the RUSP, but thinking about how we can best support the implementation of screening for all the conditions across all the states. So, I think it's a consideration we can take in that will provide us information. I hope it's not information that we feel we don't have any levers to impact. I would hope it would be something different than that.

I think the issue of having the answer come back we can do it in three years for every condition, we need something more informative, some information collected in a way that we might be able to move the process forward in a different way, and maybe it's helping states realize -- and I know they do this already. Regionalization might be the answer, so I've asked my state lab if we do this condition and if it's going to add this additional test. Do you do that now or could you do that now? And they say, no, we'd probably send it to somebody else, figure out the cost for implementing it, and see if that's feasible and then do that over time. So, that's one approach.

I think we could come up with -- the laboratory groups are talking about these are the challenges or the roadmap to implementing a new

condition in your newborn screening system and this information could help inform that as well, and it would just provide more specificity of information than I think we're currently doing now with the assessment process. Does that help? Melissa.

DR. PARISI: Melissa Parisi, NIH. So, I just had a couple quick comments. One of which was maybe you covered this, and I missed it, but why not ask each of the states if they have RUSP alignment legislation and, if so, what is the typical timeframe for adding conditions. It seems like rather than trying to discern that information in a non-discrete way, just ask the question.

But even more importantly, I mean the two-year cutoff, which to me seemed rather arbitrary, another way to potential get some of this data might be to ask states for the last three conditions that your state has added to the RUSP how long has it taken from the time they were approved to the time that you were able to add them on. I mean just another data point. I don't know if that would be helpful or not, but just another thought rather than this kind of arbitrary two-year cutoff.

DR. CALONGE: Yes, I appreciate that. I

think there are ways to ask the questions. We just came up with one for this discussion, so I appreciate that. Cindy Powell.

DR. POWELL: Cindy Powell, American College of Medical Genetics and Genomics, Org Rep. I applaud the Committee in trying to tackle this part of the decision process. One thing I wanted to bring up is regarding confirmatory testing. I think that one thing to keep in mind, that in a pilot study confirmatory testing may be included as part of the pilot. And if that may involve some sequencing of the gene or genes potentially involved and after this is put into actual practice, it may be not part of the actual newborn screening, not be done by a public health laboratory, but may be part of that follow-up and in which case coverage by Medicaid or insurers.

Often infants, even if they ultimately qualify for Medicaid, it might not be in place yet, which speaking from experience, can add a whole other level of complexity to being able to appropriately confirm newborn screening results. So, just something to keep in mind.

DR. CALONGE: Yes, that was an excellent point, Cindy. I think in this first pass, this first

draft we were trying to do more lumping than splitting. And I know there's a lot of things that we've lumped across that will vary, depending on the pilot state and how the pilot was implement versus how it would play out in actual state laboratories across the country -- sorry, state laboratories and newborn screening systems. Sue?

DR. BERRY: Sue Berry, SIMD. I think the other dichotomy that I thought would come up, but didn't, is that there are a subset of states where you can't implement anything without active legislative action on the part of the state and those states are going to be in a different subset than the people who have legislation with RUSP aligns or don't have legislation or work by rules.

If you have to do it through legislation, it takes a long time. That's why it takes so long because the last states were legislatively required to move forward. And I don't know how easily that can be captured, but it's going to slow that subset of states down more significantly.

DR. CALONGE: I really appreciate that. We're at time, but let me just ask one last -- sorry, Michele. I see you. Go ahead.

DR. CAGGANA: I'll just be quick. I know that we talked a lot about costs, and I think maybe -- you were talking about splitting, it might be really good to have the program costs versus the system costs, right, because the confirmatory testing, the treatment and all of that is downstream. And then I think states can actually use that information within their own system to be able to lobby, whatever is needed to get funding for those too, so it serves two purposes.

DR. CALONGE: Thanks. I appreciate that. Are there big considerations or questions that you didn't see? Legislation was one of them. Melissa's right. We know which states have alignment legislation, so I don't think it would be too much to say what's the timeframe for every state that has alignment issues. Although, I would be interested to know, even in alignment states, whether or not understanding the costs and requirements would be useful to state laboratories in terms of taking on implementation. Debra.

DR. FREEDENBERG: I was just going to point out that in those considerations of adding on there may be even states with alignment. There may be variables which I think may have been addressed in terms of what it would take in terms of equipment, or do you need a

whole new system set up versus can you just add that on. So, a state may choose to add something that was added onto the RUSP later, do that first because it's easier, technically, and for all of those kinds of considerations than something that requires lots of new processes in place.

DR. CALONGE: I appreciate that. I know that's true. Susan.

DR. TANKSLEY: I just wanted to comment that NewSTEPs already collects a lot of that data as far as the legislative piece and the rules and whether they're under RUSP alignment, so I think that that's a resource that could be used where it wouldn't have to be asked. But we'd have to have a mechanism to make sure all that information is updated.

DR. CALONGE: I appreciate that too. I knew it was out there. All right, you've worked so hard you've earned a 10-minute break. We're going to take 10 minutes and we'll come back and talk about considerations for the decision matrix and weighing benefits norms.

ACHDNC Decision Matrix Tool: Public Health Assessment & ACHDNC Nomination Process Update

DR. CALONGE: Thanks for coming back. We have one additional discussion that's actually split into two pieces. The first part is a proposed revision to the nomination package, kind of a redesign. This also was based on a separate working group meeting and thinking from a lot of good people, including Jeff Brosco and others. So, I'd like to present what we came up with.

Now, the comments that we heard last year were things I talked about earlier about it's burdensome, it's difficult, it's unclear, there are words used without a glossary or definition, and there are some things that seem that aren't part within the normal workflow of the advocacy organization, certainly not family. So, we tried to understand and listen around the challenges that nominators experienced. We got feedback, valuable from our advocacy, and we talked specifically to those who are currently putting new packages together or packages that are currently under consideration, including cCMV, DMD, Krabbe, MLD, and Biliary Atresia.

So again, these are slides of a draft and for revision. So, we're going to go through this, and

we'll take Committee discussion afterwards and then we're going to do audience participation and actually try to gather information and comments around what we should be thinking about when we talk about evidence and weighing evidence of benefits and harms.

So, those are the two things that we'll end the day with. And let me start with this presentation on proposed draft changes to the nomination package. Here's our current challenges: burdens on nominators, weeks and months of work go into maybe a condition that's not ready for evidence review. I talked about unclear terminology. There's no area on the nomination form to share additional information. And the workgroup, in the Nomination and Prioritization Workgroup, oftentimes doesn't have sufficient information to recommend the package to full evidence-based review.

So, here again, we're thinking about a two-step process and just trying to think about the first step as a screening process, something that is less complex, more straightforward, and can start the dialogue between HRSA staff and the Chair and Committee Members on what's necessary for nomination.

So, here are four questions for the

preliminary nomination: Is there a screening test available for use at a population level in the newborn period? Well, let me pause. If there's terms in there that need clarification like, what do you mean "available use at the population level"? So again, when we use a term of art or something that might not be as straightforward to everyone as we think it is to us, we'll make sure that we are very specific about what that means.

Is there an agreed upon way for a clinical specialist to confirm the diagnosis after a positive screen? And again, as we heard about, in a pilot program confirmatory testing may still be done at the laboratory itself or it may require a clinician outside of the newborn laboratory to do that confirmation. Regardless, is there a way to go from screening to diagnosis because they're not the same. We don't call them screening tests because they always tell you the disease. The screening test is there to tell you there could be conditions. That's where false positives and false negatives come into bear, so what do we have to do to confirm it? Is there an agreed upon way to do that? So, these first issues are talking about clarity around whether there's a test and a confirmation approach.

The next, is there a prospective population based newborn screening project that has identified at least one infant with the condition? And you'll recognize that from the previous nomination package and it is carried over into this preliminary nomination.

Then number four, does early identification newborn screening lead to better health outcomes compared to usual clinical identification? If there is not information about health outcomes from newborn screening, does early detection based on family history, such as resulting from having an older sibling with the condition lead to better health outcomes compared to usual clinical identification?

And I'll just pause around number four. It has in its history the Wilson-Young criteria for any screening test. So, the reason you screen is to say that I have an intervention that if it's applied in the otherwise asymptomatic period, that that's better in terms of health outcomes than if I wait until you have symptoms.

So, we talked about that a lot with DMD just in the last sessions today, but it's a key factor that there needs to be an answer to in thinking about moving a condition forward for nominations. If yes is there

for all questions, the nominators would then submit between one and three peer-reviewed publications for each question to the HRSA website. HRSA staff would meet with the nominators to gather information and present information to the Chair and selected Committee Members.

After hearing information and reviewing the publications, the Chair and Committee Members would provide feedback to the nominators on the readiness for Step Two. And again, there's a glossary of terms to help nominators, as I said, like what does "population level" mean. So, this is a way, is a prescreen of are you ready, are you getting ready, should you put the time into a full nomination package? And you get that feedback early on, hopefully, when the amount of effort taken to answer the four questions is still achievable and doable and not the same complexity as a full nomination.

If the answer is yes, move ahead. This looks promising. We are anxious to learn more. The complete nomination package with these sections that will go over the condition, newborn screening, net benefit of newborn screening, other considerations, references, glossary of terms, and provincial benefits

and harms of newborn screening.

The idea is to answer the questions as clearly and succinctly as possible. We don't expect nominations to be able to provide comprehensive answers to all the questions, particularly those regarding potential harms and public health impact. We had a lot of discussion about whether or not we should ask nominators about potential harms, and we decided that while the way we think about potential harms may be different than that from the advocacy community.

Assuring that you think a little bit that the nominators take the opportunity to think about potential harms, we think, would help the overall nomination package and public health impact as well. The Advisory Committee will use that information to decide whether there is enough peer-reviewed evidence of net benefit to go to a full evidence review.

For each key point you make, please identify the one or most relevant peer-reviewed references. Again, there's a glossary of terms for this, Step Two in Section Six. And then we encourage nominators to keep in touch with HRSA staff as they complete the second stage as you'll likely have questions about how to answer some of the questions.

When we talk about Section One, the condition, what is the specific condition to be screened for, the target condition, and how is it defined after screening. I realize that this sounds simple and maybe it is simpler in the newborn screening world, but not in my experience. There are conditions that have titles that there is variation in the condition under the title, so a great example is Krabbe Disease.

I think we also look at conditions that might also be picked up by the same tests as we see in Duchenne Muscular Dystrophy. One of the most key points that a lot of people, even in the non-newborn screening world, but in the preventive services world gloss over, is do you have a precise targeted definition of the condition you're wishing to screen for? So, that's what this first issue is.

How is the condition typically diagnosed now without newborn screening? So, if we didn't have a screening test, how do I say it, the more natural history of the condition in terms of when it's diagnosed. How common is the condition? That is what is the birth prevalence in the United States or some comparable population? And is it more common in certain groups in the United States, which could lead us into

questions to explore around equity.

And then again, to natural history, what is the typical progression of the condition when diagnosed without newborn screening? Here's just an aside. I said natural history, so the natural history would be what would happen if you did no treatment. So, once we diagnose things, we tend to start trying to treat them and so this is really referring to the modified natural history of disease following diagnosis.

In the next section on newborn screening, what approach is recommended? Please be specific regarding the type of sample and screening algorithm leading to diagnostic referral. So, things that are screened to with the filter paper blood spot, although challenges may be coming over time as the number of spots may be inadequate for all the conditions, we're concerned about it's only one route for diagnosis and so there have been some conditions where urine has been suspected.

I don't know how many of you know, but the first newborn screening test was for PKU, and it was by taking infant diapers and doing a chemical reaction on them to see whether or not the children were peeing out phenylketones. So, there may be other media that you

would look at. Congenital cyanotic heart disease has no sample. It has a test. It provided specific challenges to this Committee and to the implementation world because it's a point-of-service test that state labs don't do. They don't go into hospitals and put pulse-ox machines on infant fingers, so thinking about how do you collect it and what's the screening algorithm that leads to diagnostic referral.

Once there is a positive screen, how is the condition diagnosed? Specifically, what are the steps a clinician specialist would need to take to establish the condition? So, this kind of the first place where there might be harms associated with screening, so if the route from screening to diagnosis is invasive, like requires a muscle biopsy, that was just one of the first ones that came to mind, then thinking about the impact of false positives that you then have to resolve through additional testing becomes an important potential harm.

So, what are the steps to establish the condition? Are there other conditions that would be identified through the same screening as nominated, that includes phenotypes of the target conditions that are not being nominated for newborn screening like late onset or mild variants, and will screening for the

target condition identify carriers? So, all questions helping to have a sense for the Committee to think about the specificity of the screening tests in leading to the target condition diagnosis.

And then what are the approach and outcomes from population level screening for the condition? The outcomes of interests include how much there is, that is estimation of the birth prevalence, the frequency of identification of other phenotypes for a condition, screening tests characteristics, including sensitivity specificity and positive and negative predictive values.

Then in Section Three are the net benefits of newborn screening. What's the expected benefit to infants and families for the detection of the conditions through newborn screening compared to the usual clinical identification? This seems straightforward, but there is an important addition that really wasn't in the previous nomination package. It's the inclusion of the phrase "and families."

We spent a lot of time talking about that today and the concept is that benefits to families should and could be addressed with the same research rigor as other benefits. The data could be different. It could be qualitative instead of quantitative, it

might be a little bit of both, and we are interested in bringing in those additional benefits to Committee deliberations going forward.

Are there other benefits or harms that might result from implementing a state newborn screening program for the targeted condition? Do infants identify with other conditions or opportunity costs to a state public health system? What treatment and management protocols are available for newborns identified with the condition through newborn screening and is there a plan for longitudinal follow-up of newborns identified through screening? Will there be a patient registry? For how many years would infants with the condition be followed?

Section Four is other considerations, just other things that the nominators want the Advisory Committee to know and references, a glossary of terms, and then this draft section of potential benefits and harms of newborn screening drafted in a table designed to help nominators consider the full range of benefits and harms that might occur with the screening program.

This is just a slide on sample ELSI research questions, and it talked about what are the potential ethical, legal considerations for new conditions,

sources for families, clinicians, administrative databased, and then examples of questions. Do caregivers treat an infant differently when presymptomatic diagnosis is made? These are from our friend in the audience - Dr. Goldenberg, thank you very much and it's just a way of giving you some guidance or some thoughts about what questions you might add.

Committee Discussion

DR. CALONGE: So, this particular part of the discussion will be for the Committee Members and organizational representatives. And with that, I'll throw it open for questions and sit down, again recognizing this is draft. It's not been set in stone, but it is based off of a lot of the comments we heard and our current approach, so that's where we're starting from. Debra.

DR. FREEDENBERG: I was just going to expand a little bit on the benefits and harms to families. In terms of benefits to families, although I absolutely think that should be included in this important component, when you get to the operational part of it of states, when states actually think about things, they

say our enabling legislation is for newborn only and we don't really care what happens to the rest of the family because that's not within our purview. So, I just think that needs to be something we're aware of.

DR. CALONGE: I appreciate that observation. I don't appreciate it, but I understand it. That would be better. Molly.

DR. MINEAR: Can you provide a little bit more context about the collection of long-term follow-up data in terms of who would have that responsibility over time? Are you envisioning that to be the states?

DR. CALONGE: At this point, I don't envision anything, whether we could figure out a way to separately fund a patient registry across states or in some other setting, like CDC or HRSA, those would be options. It could be that the state has resources to think about -- a pilot state might have resources to think about it. It may be that in every nomination package it says, yes, this would be good, but we don't know how to do it. And I think we have to start thinking about that if we want to measure the impact of newborn screening on the health of the population from a public health standpoint over time. That's a great question with what I wish was a better answer. Shawn.

DR. MCCANDLESS: I'm just thinking about going back to the addition of the question about the family, impact on the family and I think it's very complicated and I want to make sure that we don't lose sight of the underlying principle of newborn screening. That it's intended to improve the health outcomes of the infants involved and I think that, as we heard this morning, the types of data that we will have access to around family outcomes are qualitatively quite different than the types of information we typically ask about health outcome from the infant and I just think that it's -- I don't know what I actually think about this. I'm still trying to process the concept.

I recognize that in comments I've made in the past I have specifically commented about family impacts as it relates to harms and at the same time downplayed family impacts as it relates to benefits, and I realize that there is a logical disconnect there that I have to wrap my own brain around before I can move forward with my own thinking. But I do just need to step back and say that I think that I have a real concern of a situation arising where there could be little or no personal health care benefit to the infant involved, but where the argument is that the benefit

accrues to the family driving addition of a condition to newborn screening that I think we should be really, really careful about untended consequences of changes that we make in that regard.

DR. CALONGE: And I appreciate that, Shawn, and it was one of the ways I was trying to push a little bit this morning about Don around the value statement. And admittedly, I came down to an economic value, but I meant something broader than that. How do you weigh these different benefits and the different harms in terms of thinking about the individual impact to the infant, so I think it is an area of complexity and I think the Committee needs to wrestle with that because I think there are both benefits and harms to families in terms of testing the newborns.

I'd use an example that I often use. The U.S. Preventive Services Taskforce gave lead screening in children an "I," insufficient evidence. The reason it gets an "I" is because there's nothing you could do the child you just tested for low levels of lead, other than say don't live there anymore. There's no treatment. You don't chelate. You don't provide therapy. You don't do cultural. You just say your child's been exposed. However, there's huge benefit to

the next child who can be removed from the environment prior to poisoning and so the USPSTF'S methodology has no way of accounting for anyone than the patient right in front of you.

And I think this is an area, personally. So, my opinion shouldn't drive the day, but I think from a newborn screening standpoint thinking about additional benefits, as well as additional harms, and letting those inform our decision-making could be a really important move forward. And it's how we do it that will be difficult.

DR. MCCANDLESS: To follow up, I don't know what the right answer is, but I think we need to make sure that we are thoughtful about how we prioritize the different types of data and the different benefits and harms and I think we need to continue or maybe need to have more discussion about what is the nature of a compulsory population-based newborn screening program and now is that different from other types of screening that we do and how does that impact the way that we think about the evidence-base for it. I mean it's a good point because there is nothing in the USPSTF that's compulsory. There's always a choice. Jennifer.

DR. KWON: Thanks. Jennifer Kwon, Committee

Member. So, I attended a listening group that had various individuals who had participated in the nomination package process and I will admit that I've never participated in the process, but I could tell of the people who did who are obviously very well informed about the disorder they're nominating, they felt that a lot of the culture of newborn screening and the language they saw in the package was different. And I got the sense that HRSA feels that they really support these nominators through the process, but I was also getting the feeling that maybe the nominators didn't quite feel the same way, like they felt lost.

So, one of the things that I was wondering is not so much the wording of the form, but it seems like there is a role for somebody, either at HRSA or someone who is -- I was even thinking maybe of like people who've been involved with the Committee work, but who maybe no longer active in it to maybe help nominators understand the background. I think it gets to what Shawn had brought up. I just think that sometimes people they feel that it's so obvious why they should've known about this disorder when their child was born, like so much of their life and their child's life would've been so different had they known, so obviously

it should be on newborn screening.

And they learn some basic things about newborn screening, and they realize this may be a harder hurdle than I thought and so I was just wondering a little more about the background of the process that I just don't know very much about what HRSA does when they're speaking with nominators and how long it generally takes to get them through the process.

DR. CALONGE: Jeff.

DR. BROSCO: If I may say a word?

DR. CALONGE: If it would be to the pleasure of the Committee, that'd be great.

DR. BROSCO: Just simply that in this process, Jennifer, so folks from CCMV, from DMD, from MLD, and from Biliary Atresia, the last four nominating groups that have gone through the form, we met with them and said what are all the biggest issues you've had? What are the problems going forward?

Yes, HRSA, we're supposed to be helping you through this process. It's clearly not going as well. WE heard from them it takes a huge amount of time and energy and just emotional to get through this huge thing, only to find out that maybe we weren't ready or something. So, in the two-step process, we really tried

to figure out how we can both meet the needs of nominators, but also not slow the process down so much. So, this is an attempt to do that is to meet the needs of nominators so we can quickly get to what are the key things and so the idea of those initial four questions is we gather the information, we present it to the Committee, which is usually the Chair and a couple Members and then there's some right away back and forth.

So, there's a very low initial bar for nominators to get a sense of, yes, we're ready. Let's go for it or, no, we really need to have a treatment. We need a better test, whatever that is. So, that was the idea because you're right. That's exactly what we heard too is that nominators we're there to help, but it hasn't been sufficient.

DR. CALONGE: Ash.

DR. LAL: I was just looking at the other sections, so Section Seven has the table Potential Benefits and Harms. I can definitely see the utility, I think, if the nominators upfront address some of the questions regarding harm in addition to the advocacy for including the condition. That would certainly move the process along. But my question is, is this table something that will be included from published

literature or is this something that is currently being developed and if it could be shared for comments.

DR. CALONGE: No, everything here is to be shared for comments. I'm sorry, Jeff, did you have another comment?

DR. BROSCO: Sorry. Jeff Brosco again. So, just that table that comes from a publication that Aaron was the chief and it's there as an appendix kind of thing. If nominators wanted to look at the kinds of issues that might be relevant, they could use that as a tool, but it's not meant to be comprehensive.

And just to add one other thing, we also learned in talking to the nominators that we couldn't predict ahead of time all the kinds of questions that they would have and so that's why this having plenty of room for dialogue early on and saying you don't have to put in anything about public health impacts or harms, but if you know something about it, you can. If you're planning a patient registry, please tell us. But if you're not, that's okay to say no. So, it really was meant to create a dialogue.

DR. CALONGE: Thanks. Jannine.

DR. CODY: I guess my question really is for Jeff and his comment that he just made. Is there some

sort of instruction booklet or something that groups can know that when they see this daunting list of questions that you don't have to have a publication that addresses that, but if you know of one, tell us, the ones that are optional versus the ones that are not?

And I could well imagine that groups get very focused on the medical, the treatment, the diagnosis part and could get to this point of thinking they're ready for a nomination package and realizing there are questions in here we could've been working to address those. We just didn't know we were going to get asked that and they could have facilitated the research around that question, especially the family questions and the sibling questions and the registry questions.

And so, I don't know what is available or if there should be more available for really advanced, maybe the groups that are five years out to know what it is that they're going to face and the kinds of questions they'll address before they even talk to a HRSA person.

DR. CALONGE: I mean I appreciate that. I do think a user's guide is something that would be relatively easy for us to put together. Again, the kind of Step One questions are meant to say, what should I be thinking about, in terms of answering these first core

four questions, which will help guide whether or not this condition is ready to be brought forward or what else is going to be needed. And it's answering those first four that I think HRSA, and the Chair say, yes, it looks like this is ready for more detail that you'd move onto Step Two with more detailed questions.

And again, I think there would be another set of guidance on how to fill those out. I like your idea of saying this one has to be answered and I think ought to think about that and these other ones are discretionary but could help HRSA think about the condition and would be useful for nomination and prioritization in assess the evidence and thinking about it's ready to move on for evidence review. All right, I have Natasha next.

MS. BONHOMME: Thanks. Natasha Bonhomme, Genetic Alliance. Tied to the part of the conversation with Jennifer and Jeff talking about the support for nominators, and just to acknowledge that there is a lot that happens to support those nominators outside of the HRSA framework, even though we know that that is what we're talking about here today. Those nominators are very well connected with each other. They study the nominations that have come before. I don't think there

is any group that just wakes up one day and says, you know what I'm going to do? I'm going to dedicate nine months to filling out this process, to filling out the nomination. So, I just really wanted to acknowledge that between also us having invited Committee Members to the boot camp that his cohosted between Every Life and Expecting Health, but there's a lot else that goes on and maybe there's some learning there too in terms of those conversations that have been supportive and what could be even more supportive for those nominators, so I just wanted to acknowledge all of that other work that goes on.

And then my question was to -- and I know these are draft, but I was thinking to the Step One preliminary nomination, and this is just an example of, but where it says in Question Three. Is there a perspective population-based newborn screening project? Is that globally? I think, historically, we've always looked for the U.S., those types of details, are you thinking of adding in those details as this moves from draft to final or not? I just want to be clear where are the things that may be assumptions like, of course, it would be a state-based newborn screening program or maybe it is an assumption, maybe it is global.

DR. CALONGE: That's a level of specificity that will be added that hasn't been yet, so good question. Thanks. Robert.

DR. OSTRANDER: Robert Ostrander, American Academy of Family Physicians. I want to just go back to the way we think about the family benefit piece and Shawn's concerns. For the first 20 odd years that I was in practice, I did family-centered obstetrics and delivered babies and rarely did I consider the baby's benefits and harms separate from the mother's and the mother's benefits and harms separate from the baby's benefits and harms. And I don't think the moment of delivery completely breaks that link, so I think when we're thinking about newborns and how medical homes for kids with special health care needs it would be an unusual situation where there was a benefit to the family that I didn't think benefited the child, and not that one couldn't think of things.

And furthermore, I think if there were no benefit to the child for disease treatment, whether medically specific disease treatment or general treatments that modified the course of the disease, I can't imagine that the assessment of family benefit would be positive because I think the place that

everybody's seeing potential family harm is the false positive screen, the variant of unknown significance, or the diagnosis of it a disease for which there's treatment.

So, I think we have to be vigilant. I agree, Shawn. I think we have to be sure that there is a net benefit to the child, but again, I think it would be rare, in my mind, to see a net benefit to the family that didn't somehow also then confer benefit to the child.

DR. CALONGE: I think we're moving into what we would expect would be the last discussion of the day, which I think is a natural movement. I think we did get a lot of comments about what benefits and what harms should be considered and I think what we're hoping for the last discussion is just talking about when we're weighing certainty and net benefit what are the full range of relevant peer-reviewed evidence we should be looking at.

Most of the evidence we've looked at is in relationship to benefits and harms to the individual and those are still paramount, but the Committee should consider benefits and harms to the family and to society, at large, including looking at issues around

equity. Should the Committee consider evidence demonstrating benefits for the family regarding future planning in terms of finances, geographic proximity to services, home design, should there be earlier access to Early Intervention programs or are there opportunity costs to the public health system, and that comes back to the issues overall how is funding constructed for newborn screening in a state and it only varies 50 time, even in states with alignment regulations.

So, before we launch down this, let me make sure I go back to Margie and get her comment.

DR. REAM: Thanks. Margie Ream, Child Neurology Society. So, I had a question back to the nomination form. I think it was in your first of those two presentations where there was a line about other conditions that could be picked up or other phenotypes that could be picked up by the proposed screening.

So, the question, and a story. So, the question is how the Committee feels where the line would be drawn between something being a secondary condition, which would be considered beneficial to pick up, versus a false positive, which would be generally considered unwanted.

And so, the story I have to frame why I had

that question in my mind was taking, for example, XALD. I got a baby girl screened positive. She's diagnosed and then we can diagnose her brothers. That would be beneficial. But if a younger sister of a symptomatically diagnosed boy came and the family wanted the younger sister tested, I wouldn't offer that testing because that wouldn't be considered ethical. It wouldn't help that individual patient. And so, same condition, same diagnosis, but one diagnosis through mandatory testing is positive, where a clinically requested diagnosis would not be considered a positive. So, as a clinician, that's a tricky situation to be in. You have the same question of the baby girl is in neighboring rooms, basically.

So, back to my question for the Committee, what are some of the considerations you would use for when one of these other diagnosed conditions would be a secondary target versus a false positive?

DR. CALONGE: That's a great question and it's also partially a subject that's being looked at by a laboratory workgroup on secondary conditions and condition counting and a level of complexity that I hope we would be able to capture in the nomination package.

In the other areas like USPSTF or the CPSTF,

there are these things called "other benefits." And so, if I'm doing this one thing and I find something else that might also benefit from that or I'm doing a treatment that treats one thing, but there are additional benefits, how do you capture those and how does that drive decision-making?

So, I think making sure the nomination package has the ability to have that flexibility over other conditions that could be treated and helpful I think they could be answered, but it would kind of in that "other benefits" considerations, if that helps. And that's what we're talking about, a lot of, other benefits. I think one of the things that comes up in genetic testing, which that reminds me of, is evidence by analogy.

And so, are there other gene polymorphisms that look so much like the polymorphism for which you have evidence. Do you think it's reasonable to make a decision by analogy? And so, in this space would there be conditions that aren't the condition under review, but that we could consider other disorders because it's relevant to that condition. So, those are the kinds of areas we want to first ask the Committee and then our organizational reps and then throw it open to the rest

of the audience.

What are the kinds of things that we should include around family history? I keep talking about opportunity costs and in a severe tax limitation state like Colorado it's a real issue. We would not be able to add a condition in the next two years that would cost any money because there's no money for the next two years. That's like, okay, I got that. So, that's an opportunity cost. What are you going to not do, how are you going to address the overall system that has to respond to many, many important public health needs, one of which is newborn screening? So, that's the kind of opportunity cost issue which maybe doesn't occur to everybody, but I think about quite often.

So, we are thinking about considering the full range of peer-reviewed evidence. And the concept is we wouldn't use a lesser bar to evaluate qualitative research or research on these other family-related outcomes. We don't need to and so the idea is that we want evidence-based evidence. We will prioritize the individual child, but we could also look at benefits and harms to the family, to society, and make sure we consider equity, and I talked about these three issues.

And then, harms and benefits should be

supported by peer-reviewed evidence directly relevant to the consideration under review; however, can we learn things from other conditions that might help the Committee in making its decision? So, now I'll pause and maybe we've all talked these out in the Committee so far, but are there additional thoughts from the Committee or the organizational reps? Shawn.

DR. MCCANDLESS: Shawn McCandless, Committee Member. So, I'm looking at the last bullet point, "Harms and benefits should be supported by peer-reviewed evidence directly relevant to the condition under review." Part of the problem that we constantly have is that there is little to no significant research about harms. People can point to a couple of ongoing studies and specific individual studies that, for a couple of conditions, are trying to assess harms.

I just want to be thoughtful that we're not creating a bar here, the evidence-based requirement for hypothetical harms that can't be met with the current system. Because one way to interpret that would be to say unless there is a peer-reviewed document, peer-reviewed paper that demonstrates harm we shouldn't consider that and that would be ideal. But I think for both benefits and harms it's important to keep in mind

that there are going to be some potential, and maybe potential and obvious or maybe potential and less obvious harms and benefits that we still need to be able to think about, in my opinion.

DR. CALONGE: And maybe the underline is too dramatic. I would point to, though, the use of the word "should," and maybe it's really ideal it should, and we need to be open to thinking about where the evidence is less strong, but the potential for harm is still great. Okay.

Public Discussion

DR. CALONGE So, is there anyone in the audience who would be interested in coming up to the microphone and giving us a thought about potential benefits and harms? And if you could just identify yourself for the record, that would be great.

DR. ELLINWOOD: Thank you. I'm Matthew Ellinwood. I'm the Chief Scientific Officer at the National MPS Society. We have the distinction of actually having written two successful nominations to the RUSP. I have written one. I would observe that the current form is just two years old. It's two years and one month old and I don't know that the considerations

for changes really gives you much greater flexibility for advocacy organizations to fulfill.

HRSA worked very well with us. It was about a nine-month period for us to work out the kinks to get our MPSII nomination in. Regarding harms and benefits, I'd like to echo what Shawn said. Let's just try a thought experiment. A year to get agencies to approve funding for research, a year to get the applications in and get them approved, two to three years to do the research, we're talking five years before there is a body of literature that helps support information on this.

We're already creating more bars than we need to for advocacy or organizations to get things through. There are family benefits. There are family harms. I think for the most part the family harms are associated with the false positive diagnosis. I would concentrate more on that. This is never going to be a body of information you're going to have conclusive research on. It's just too difficult to do. With rare disease, we cannot get the level of epidemiologically accurate information in our kind of atomized health care delivery system. It's just going to be too problematic.

I'd also like to put a pitch to the

Committee. Reconsider the N-of-1 rule. There is no need for one perspective program to screen and identify and confirm and treat a patient when all of those elements can be provided in parallel rather than series. If we have not learned anything from COVID, we move faster when elements of any scientific medical problem are chopped up so we can pursue them in parallel rather than in series.

We are, indeed, right testing a system, Scott, but testing a system in North Carolina is not going to be the same system that gets instituted in Ankony and Iowa City and Denver and Phoenix, so, okay, enough of that. Thank you.

DR. CALONGE: Thank you. Next--and please identify yourself.

MS. Brackbill: Lesa Brackbill, Leukodystrophy Newborn Screening Action Network, but also a Krabbe Disease mother. When discussing the harms and the benefits, I just want to remind you all from the family perspective that no matter when the child is diagnosed, whether it is through newborn screening or symptomatically, the family has to deal with that reality, and I believe the harm is far less when it comes through newborn screening because the family has

options.

Otherwise, like in our case, our only option is to watch our child die a painful and long-suffering death, so no matter what we are harmed, but we have to look at what harm is less. I love that you did mention that there are psychological benefits and harms. We are more likely to have things like PTSD, things like that from our child's diagnosis when it's symptomatic and so I understand we have to take all of this into consideration, but I just want to make sure that those of us who didn't have the benefit of newborn screening that our voices are heard as well.

The other thing I wanted to say, as we always say, it is just a screening, so the parents get to choose what to do with that information. They're not forced to treat their child, but they're given those options, which I believe is a benefit greater than any of these harms. Thank you.

DR. CALONGE: Thank you. Please identify yourself.

MS. GAVIGLIO: Amy Gaviglio, I'm a genetic counselor and consultant for a number of organizations in the newborn screening space. For me, I think, as we think about benefits and harms, and I'm really glad that

the discussion is around what does evidence look like for both of these, but I think what feels like is missing -- and maybe this gets to some of your questions, Dr. McCandless, is but how is it actually going to be used in the decision matrix? What is the threshold? How much do we need to show more benefit than harm and how do we set up a system so that that remains constant, and that decision isn't dictated by who's on the Committee and who feels harms are more evident than benefits.

So, I think really thinking about this discussion, not just in what should we be collecting as it pertains to evidence for benefits and harms, but being very clear then in how that is actually going to be plugged consistently into the decision matrix will be really helpful for advocates who are trying to submit a nomination and I think often feel like the goal post moves as we talk about benefits and harms. So, I'd just encourage a lot of that discussion on not just what we're collecting, but then how you're going to actually think about benefits and harms as it pertains to the matrix and what is that threshold for a yes-no vote.

DR. CALONGE: Thank you. Yes, please identify yourself.

DR. BAILEY: Don Bailey, RTI International. So, first I think I need to say I think most people know that I'm on the National Academy of Sciences Committee. I need to be very careful about saying things that are giving advice because I am making sure it's not advice coming from the National Academy of Sciences Committee. It's a personal opinion.

So, I'm here today just saying, as you might expect, I really appreciate the thinking about expanded considerations of harms and benefits. And I think that's especially important when there's a close call. Like with the Krabbe vote, it's seven to seven. People came in with different values and different perspectives in weighing harms and benefits in different kinds of ways. And thinking about those maybe a little more broadly could've helped push the decision either way, so doing it in a comprehensive way is especially important.

I wanted to say that there might be a set of harms, and this is going to the last one and to your comment a bit, Shawn, to a set of harms that we will never be able to answer the harms and maybe benefits to, but I'll just focus on harms for a minute. That we'll never be able to answer on a condition-by-condition basis. But there may be some general harms that have

been brought up over and over again, like harms about uncertainty about later onset, harms about false positives, harms about carrier detection.

There could be a collection of information that's gathered about those topics that then could be used as the Committee is having these discussions that doesn't necessarily -- you could then bring it to discussion for this particular disorder, but having that knowledge base that says, in general, here's what we know about anxiety about uncertainty and here's what could be done to mitigate it, then that could help maybe inform or answer some of the questions about the harms that are otherwise brought up to that particular disorder when it may have been answered in number of other context and not just this particular one. Thank you.

DR. CALONGE: Thank you. Please identify yourself for the record.

MR. SIMON: Hi. Good afternoon. My name is Dylan Simon with the Ever Life Foundation for Diseases. I do want to take a moment before I go into my comments just to thank the Committee for this opportunity before I comment. The patient community has long asked to be able to engage more directly with this Committee, and

from the listening sessions of last year to this comment session this is much appreciated. I can hear from the tone it creates confidence.

For me, personally, I want to bring up a couple points to Dr. McCandless' point in terms of setting high bars. I think what we need to think about is in addition to the benefit of harms, when reviewing the package, potential harms is setting too high a bar that a community cannot submit a package in and of itself.

So, when we're talking about the harms and benefits should be specific to an individual's condition, I know you said that is a preferred method and understanding that that may not be possible, but when communities are going to be looking at that on the website and may not speak directly to HRSA first. Their interaction is going to be on the website. They're going to see that and say, well, there's no world in which I can develop family benefits and harms in my community. And so, you're going to see communities not even attempt to submit a package and we're well aware that there are significant harms to that to many within the community to think that it's not even possible. That newborn screening to them is not even possible at

the federal level.

So, I want to make sure to recognize that there needs to be a high evidentiary standard and we're not here recommending lowering that, but every time you add a new bar, you're making it harder and harder for members of the community to submit a package. And to the point that Natasha Bonhomme made earlier, there's already so much that the community is doing, whether it be pilot studies or helping to support the development of diagnostics and therapeutics, when you add more requirements on top of that, that will require more resources, more funding, more manpower, you're going to lose communities along the way that don't have that. So, I just urge the Committee to keep that in mind as well. Thank you.

DR. CALONGE: Thank you. Shawn.

DR. MCCANDLESS: Shawn McCandless, Committee Member. I think this is an opportunity, I think, to thank the people that did the hard work on this because it does seem to me that the proposal that's been made to have a preliminary, simpler approach to kind of ticking the first set of boxes. To me, that does seem to level the playing field and it does reduce the burden for groups that may not have for very rare diseases where

it's a smaller number of people involved or where there's not pharmaceutical companies that are supporting the effort to develop newborn screening packages.

It seems to me that that levels the playing field and does help a smaller community or a less well-resourced community kind of at least get over the initial activation and energy of is this even feasible. And so, I think you all should be congratulated for the work that was done because I think this proposal is an improvement over the existing system and then it also sounds like that the process will be more clearcut and therefore the support from HRSA and from other groups should be able to be more clearcut and helpful to again reduce the activation energy for those less well-resourced conditions and support groups that are advocating for newborn screening. So, to me, it seems like a really good opportunity to say to the people who did the work here I think this is actually a step in the right direction.

DR. CALONGE: Thanks, Shawn. And I think we did talk a long time about that last table -- never mind. Natasha, you go next.

MS. BONHOMME: Are you sure you don't want to finish your thought?

DR. CALONGE: I'll remember it.

MS. BONHOMME: Natasha Bonhomme, Genetic Alliance. A question that I had, as the Committee or Ad Hoc Group was discussing harms and benefits, how much discussion went into deciphering between harms and benefits of the information versus the process versus the communication because we have so much of that hearing from families who have gone through, let's say, a false positive who it really so much was how the information was delivered. So, it's not so much you had a false positive, but it was the how that really caused the harm or made it become such a particularly negative, extended negative moment as opposed to a "that was hard, but I worked with my pediatrician, and we were able to figure it out." I'm trying to think where that fits in since for the limited research that we have done in this space that comes up all the time and that is not about a particular condition or a particular screening modality, so I don't know if that came up in the discussion as you were putting this together.

DR. CALONGE: I don't think we thought about it that specifically. I did this morning, though, when I heard presentations on service versus outcomes and so that was really important for me to hear, so we're

broadening that concept of what could be there. Susan.

DR. TANKSLEY: Susan Tanksley, Association of Public Health Labs. Maybe a simple question. I'm just wondering how this process in reevaluating the nomination process lines up with the work that NASEM is doing in what the timelines are for those.

DR. CALONGE: I think the NASEM study could inform this. I also know that NASEM studies take a while, having been on several of them, so I feel like the next version of the nomination package has a chance of going into the field prior to that report coming out, but maybe I'll be wrong, so I appreciate the concept. You're right. They're talking about the things we're talking about. Dean.

DR. SUHR: Dean Suhr, MLD Foundation. I'd just like to echo what Dillon started us off with, which is thank you for including us in the conversation and having a dialogue. This is very reinforcing because this package ultimately is for us, the community, the advocacy groups and so to have a voice and input is appreciated.

Dr. McCandless, I just wanted to reflect on your comment about leveling the playing field. Respectfully, I think Natasha mentioned this, but also

with what EveryLife and Expecting Health are doing. The boot camps, and those kinds of environments. It amazes me. I was a speaker at one of the earlier ones and attended a number of the others. It amazes me the number of groups that are coming there to figure out how to do newborn screening.

And the message, as they walk away, is certainly as we engage with them is not you can't do this, but let's talk about how you can and what are the problems and what are the challenges, so there's a lot of help out there for them.

I've talked about harms and benefits before. I want to apply that to a different group. I want to apply that to the Committee. I want to make sure, because we've talked over the past few years of the tsunami of potential nominations coming your way. I want to make sure that what appears to be a steppingstone process, and mind you, I haven't seen the forms, I haven't quite grasped all of this, but how this process which you reflected should make it easier for us, or step-by-step. By the way, I'd never take a first step without knowing what the next three or four are because either I don't want to waste my time, or I don't want to get my ducks in a line so that I didn't get a

partial yes or a partial no, early on.

But what does this mean to the Committee and your engagement along the way? Is it more work, does it take more time to talk about MLD or any other disorder two or three times instead of one or two times? I think we ought to be thinking about that in that context too because throughput of your committee, throughput of the evidence review, and now the nomination and prioritization, which again I'm not quite sure how that fits in here with this intermediate step, but I just want to give the grace, I would say, that it's not all about us. It's about you as well, and we, as an ecosystem, need to work efficiently together.

DR. CALONGE: Thanks. What I was going to say was we talked a lot about whether we should ask nominators to fill out the table and I'll try to say it again. It wasn't meant to be a bar, and maybe that needs to be in the explanation. You may want to think about this. And so, the idea is that nominators are thinking about potential harms and benefits, but recognize that that's what the evidence review for, not only are they going to find that, but they're going to quantify it, which gets me to my second point.

The way to consider family benefits and

additional harms is through evidence, and so the evidence bar still needs to be there for saying we believe there are family benefits associated with this. The issue about harms is that we don't routinely look at harms, but I think thinking about how appropriately to think about harms and I think that we could often, at least, apply numbers to them because we have quantitated estimates of false positives and false negative and predicted values that could be attached to most tests.

But to always think that it's an evidence-based approach is just -- I think what we're trying to do by saying supported by peer-reviewed evidence, so I don't want to make you think that if we're going to consider family values, they're not going to need to meet an evidence bar. But what I will say is if they're not in the nomination package, they don't have to be in the nomination package. It's very clear that all of the benefits might accrue to the individual child themselves, in which case that's plenty, right, for sorting through thinking about the evidence and looking at risk benefits. And we'll have to deal with the issue about the harms associated that we don't measure well and that we do worry about.

Purposefully, the come in the U.S.

Preventive Service Taskforce every review, so it's just something to keep in mind. And the last thing is that I actually think this dialogue with HRSA staff early is going to help. So, maybe you're already thinking about Steps Three and Four, but would you like some guidance on Questions One, Two, Three, and Four that might help you as an advocate or a family move a little farther ahead.

The last issue about the tsunami, as I expected, is going to come after I leave, which is fine. No, I think we're thinking about that as well with the prioritization strategies that Dr. Kemper in the evidence-based review has thought about. And as that actually hits, I think the Committee will adapt its processes, its size, it's staffing to accommodate any real incredible increase in the number of conditions that come to us at one time.

I feel like we adapt. We're adapting now. The issue about you've only had this for two years. I read a nomination package that came out of that and it needed to be revised, so I just know that. So, we want to be a learning community. I would say this is a refinement of our processes, not a redesign and we'll try it, and we will find the issues that don't work as

well as we'd hoped they would and then we'll refine them again.

But it always has to be, like we're doing now, in contact with the people trying to put together nomination packages so that we can look at them in a timely fashion and get our decision-making in a more timely way. So, I hope that helps.

Michael, do you have anything you want to add to the discussion? Sorry, I always have to pick on Michael.

DR. WARREN: I appreciate the conversation today and I just want to reflect on the last part and this notion of the tsunami of potential nominations and I appreciate the mention from the speaker earlier. I do think the pragmatist in me does think a lot about what does look like from a HRSA staffing and resource standpoint and so I think it's helpful to at least state on the record what those limitations are.

The budget for the Inheritable Disorders legislative authority, the current budget outlook, all of those factors come into play and there's not just a situation where the Committee wants to change this process, go hire five more FTEs. I wish that were the case. So, we will have to navigate that as it comes.

And I think we feel very strongly that having more engagement, being more transparent, and in particular engaging families more, is the right thing to do and so we want to at least have this dialogue and understand what the needs and desires are and then, do the best we can, figure out how to make that happen.

DR. CALONGE: Thanks. Do not forget there will be a Federal Registry posted for people to provide written comments on what we've talked about today. I hope those of you who wanted to think a bit about it first will do that and people who are online I think might want to do that as well. I will pause since we're not quite at time to see if there are any online public comments. And again, I'm not certain of the process. I just know we won't see you, so someone is figuring out that you're there. And while we're waiting, please identify yourself.

MR. SIMON: Dylan Simon from Ever Life Foundation again. Happy to kill a little time while those online find the raised hand function. One thing I did want to flag, I know we're not going to get into logistics today, but as you decide this, recognize what the implementation timeline for this will be. There are multiple communities right now who are preparing

packages and they're waiting until the May pause. That's understandable, what's talked about here and in the previous slides about new requirements needed for the data and if that's brand new information those communities need to collect, there needs to be a thought processing to how are we going to phase in this implementation to ensure the fact that a community that has a package ready to go on May 15th now, all of a sudden, doesn't have to take another year and a half to go collect new data and so what does that process look like. And they can look at a variety of ways, but they just want to flag as logistic as you get into the details to look at it. Thank you.

DR. CALONGE: Appreciate it. Thanks. And so, noted. So, I think we have no comments provided online, so -- I have Michael Gelb raised a hand. Michael.

DR. GELB: There's a lot of talk about harms and benefits and I just want to say things have gotten better in the last five years. I don't know what all these harms are that you're talking about. I mean Shawn McCandless talked about a Krabbe story where the family got ruined because of a false positive. I mean those days are long gone with second tier markers like

psychosine and glycosaminoglycans for MPS1 there essentially is no false positives. Now, there is late onset disease, but with these biomarkers, we're pretty sure that late onset disease is coming in the first one or two decades of life. And so, I think from MLD there is no false positives and there is no false negative and it's all published, so I think we need to go a little bit easy on all the harms discussions when things coming there isn't any harms essentially. The tests are nearly perfect if we do them right.

And I think it's important that newborn screening labs take on second tier test or at least that it gets done, but we see a mixture of uptake in newborn screening labs refusing to do second tier tests, like in Ohio they don't do psychosine. I mean it's crazy, so we need to get better at that. Thank you.

DR. CALONGE: All right, I think we've come to the end of the agenda. I want to pause again and first of all thank all of our speakers. The presentations were outstanding, gave us a lot to think about, filled in some gaps for at least some of us, and I can only tell you how much I look forward to, Don, to your instrument as it rolls out, as you get more experienced and you generate data that we can use to

assess family impact of screening, treatment, and other things associated with newborn screening. Great. I really appreciated Aaron coming and being here with us in person and having to watch your team lose from Rockville, but your presentation didn't suffer a moment. It was absolutely great, as was Dr. Ackerman's and really, I think helped move us all forward in our thinking.

Alex, I appreciate the update on DMD. I know we're all anxious about the upcoming presentation and that will be fantastic to hear as well. I appreciate the input of all the people who served on the working groups to provide the draft slides that you saw today and active discussion that will help guide changes and help us fill in the blanks of all the things we forgot to include because that's what presenting provides.

And then, finally, for the public comment periods, I realize it's difficult for many people, if not most people, to speak in front of a group of people. For some people it's the worst, scariest thing you'll ever do, and everyone was so accomplished at it. I appreciate the time, effort, and the shared experiences and knowledge that brought forward. And the last thing

I would say is thanks to everyone who made a public comment. I think you showed us that's something we could do. We could probably do on a regular basis in that more interactive forum, as we did at the end, especially when there's specific topics where that kind of more free flow of information and dialogue can be beneficial to the Committee in its learning and it's doing its work.

So, it's not like we're done yet. We have a full day tomorrow. We have very important public comment period and expedited evidence review and discussion, a vote on Krabbe Disease, and there is just so you don't leave early, an APHL presentation after the vote. Did I miss anything? Leticia? It's been a great day. Thanks so much for your time and have a good evening.

(Whereupon the meeting was adjourned at 4:11 p.m., to reconvene on Tuesday, January 30, 2024, at 10:00 a.m.)