THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS 5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Thursday November 2, 2023

10:00 a.m.

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P R O C E E D I N G S

Welcome and Roll Call

DR. CALONGE: Good morning, everyone, and welcome to the last meeting of the Advisory Committee on Heritable Disorders in Newborns and Children in 2023. I'm Ned Calonge, Committee Chair. I just want to say it was great seeing so many of you at the APHLISNS Newborn Screening Symposium meeting in Sacramento.

I thought we had a great dialogue during the Advisory Committee session, as well as other morning sessions, and any others I was fortunate enough to participate in. I now need to transition to Leticia, who's going to do our roll call this morning.

COMMANDER MANNING: Thank you, Ned. Good morning everyone. From the Agency for Healthcare Research and Quality, Kamila Mistry? Michele Caggana?

DR. CAGGANA: Good morning everyone, here.

COMMANDER MANNING: Carla Cuthbert?

DR. CUTHBERT: I'm here.

COMMANDER MANNING: Janine Cody?

DR. CODY: I'm here.

COMMANDER MANNING: Christine Dorley? Jeff Brosco?

DR. BROSCO: Here.
COMMANDER MANNING: Jennifer Kwon?
DR. KWON: Here.
COMMANDER MANNING: Ashutosh Lal?
DR. LAL: Here.
COMMANDER MANNING: Shawn McCandless?
DR. MCCANDLESS: Here.
COMMANDER MANNING: Mollie Manier?
DR. MANIER: Here.
COMMANDER MANNING: And Chanika Phornphutkul?
DR. PHORNPHUTKUL: Here.
COMMANDER MANNING: And for our organizational representatives, Robert Ostrander?
DR. OSTRANDER: Here.
COMMANDER MANNING: From the AAP, Debra Freedenberg? Cynthia Powell, or Cindy Powell?
DR. POWELL: Here.
COMMANDER MANNING: Steven Ralson? I think I saw him on. Karin Downs?
DR. DOWNS: Here.
COMMANDER MANNING: Susan Tanksley?
DR. TANKSLEY: Here.
COMMANDER MANNING: Scott Shone?
DR. SHONE: Here.
COMMANDER MANNING: Shakira Henderson?

Margie Ream?

DR. REAM: Here.

COMMANDER MANNING: Jacob Hogue? Natasha Bonhomme?

MS. BONHOMME: Here.

COMMANDER MANNING: Siobhan Dolan?

DR. DOLAN: Here.

COMMANDER MANNING: Cate Walsh Vockley?

DR. VOCKLEY: Here.

COMMANDER MANNING: And Sue Berry?

DR. BERRY: I'm here. Thank you.

COMMANDER MANNING: Thank you all. Is there anyone that I missed on the roll call?

DR. CAPOSINO: This is Paula Caposino from FDA. I'm also here.

COMMANDER MANNING: Yes. Thank you.

DR. CAPOSINO: Thanks.

COMMANDER MANNING: Now I'm just going to go over a couple of reminders. The first is our conflict of interest reminder. Committee Members, please recuse yourself from participation in all particular matters likely to affect the financial interests of an organization, with which you serve as an officer, a director, trustee, or general partner, unless you are also an employee of the organization, or unless you have received the waiver from HHS

authorizing you to participate.

There are no votes scheduled for today, but if there is some content, or some issue where you think there may be some type of conflict of interest, please notify me immediately, and you can email me at lmanning@hrsa.gov.

For meeting participation, according to FACA, or F-A-C-A, all Committee meetings are open to the public. If the public wish to participate in the discussion, the procedures for doing so are published in the Federal Register, and are announced at the opening of a meeting.

For this meeting, the November meeting, in the Federal Register notice we said that there would be a public comment period, and only with advanced approval of the Chair or the Designated Federal Official may public participants question Committee members, or other presenters.

Public participants may also submit written statements, and 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 a 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 Officials. Just a little housekeeping note for the webinar. Most of you are clearly logged into Zoom, but if you would like to change your name you'll be prompted to enter your name as you would like it to appear on the Zoom display.

To ensure the meeting host can easily identify you, please use your first and last name, along with your relevant organization name. If you have any technical issues, please email Emma Kelly at ekelly. E-K-E-L-L-Y @lrginc.com. Next slide please for the meeting dates.

So this is our schedule for 2024. There is a very strong likelihood that the dates for February will change. So currently it's scheduled for February 8th and 9th, but you can check back on our website, and it will be updated if there's any change to that date. And now I turn it over to Ned.

DR. CALONGE: Thanks Leticia. Next slide please. You'll remember that in previous meetings I talked about that the National Center for Newborn Screening Excellence, or NBS Excel was awarded to support the NBS Propel grantees, and other NBS

programs by providing leadership, technical assistance and quality improvement expertise.

Last week, NBS Excel announced the establishment of a Newborn Screening Follow-up and Education Subcommittee. An invitation was released, soliciting applications from NBS program staff, families, educators, and medical specialists with professional and/or lived experiences in short-term follow-up, long-term follow-up, and provider and family education.

These are to serve as members of subcommittees and work groups. We ask that you contact APHL with questions. The applications are due tomorrow on November 3rd. As a reminder, please keep a lookout during the next weeks for the NBS Co-Propel Program. NBS Co-Propel builds on a previously funded HRSA grant program to strengthen collaborations between state and territory public health agencies.

And with NBS partners, such as universities, nonprofits, or other institutions with expertise in newborn screening, to achieve a common goal. And that is to improve access to services and outcomes for children identified with a heritable condition identified through NBS, so that they are healthy, growing and thriving. Please check

grants.gov for updates, including the NOFO, I'm sorry, the N-O-F-O, or NOFO, and deadlines once it is available. Next slide please.

I think we mentioned this briefly, the National Academies of Sciences, Engineering and Medicine, that we also call NASEM, is seeking suggestions for experts to participate in a new study, newborn screening, current landscape and future directions.

The resulting committee of experts will conduct a study to examine the current landscape of newborn screening systems, processes and research in the U.S., and consider sustainable options of screening for new conditions, using new technologies.

They expect to recruit 12 to 15 volunteer experts to serve on the Committee. In addition to collecting information for potential speakers, participants, and peer reviewers for any publications resulting from this activity. They're specifically looking for expertise in the following areas: public health screening at the state or federal levels, including screening for the Recommended Uniform Screening Panel, and the review of that.

They're looking for experts in patients and family lived experiences, looking for experts in clinical care, including screening, return of

results, and follow-up care,also, existing and emerging technologies for newborn screening, clinical lab practice, bioethics, including privacy, legal and equity, and access issues, data collection sharing and use, health economics coverage and reimbursement.

And we ask that you, if you think about submitting a nomination, that needs to occur by November 17th of this year. If you can't figure out how to submit a nomination via the website, I'd ask you to contact Leticia, who can help you navigate that process.

With those announcements, we're going to turn to Committee business. In September we received a nomination package for biliary atresia. The lead nominator for the application is BARE or B-A-R-E, Inc., a national nonprofit organization that supports biliary atresia research and education.

You may be aware that biliary atresia is a congenital liver disease characterized by obstruction of the extra hepatic bile ducts, and impair bile flow out of the liver. The nomination package is currently under review by the team of HRSA. As a reminder the nomination package is reviewed to ensure it meets three core requirements: validation of the laboratory test, widely available confirmatory testing with a sensitive and specific diagnostic

test, and a prospective population-based pilot study.

We work closely with the nominator to ensure that the package is complete, and contains supporting references and data that support answers provided on the nomination form, and via the nomination process. Prior to sending it to the Nomination and Prioritization work group. Next slide please.

We did send out a 2023 meeting summary, and I appreciate Committee members reading through that and providing comments. There were some comments that we're incorporating into a revision of the minutes, that I think we'll send out today, and then we'll formally vote on this tomorrow.

So I'll ask for any other meeting corrections at this time, and then hopefully you'll all review the revised version, and we'll remember to vote on that tomorrow. So I'll pause to see if there are any other comments.

Seeing nothing in the chat, can I have the next slide please? So what are we going to do today. Here's our agenda for just today. We're going to have an update on a recent National Academy workshop with Committee decision. We're going to hold our public comment today, and then we're going to have discussions on the Decision Matrix Tool, and the

proposal for our conflict of interest approach.

We're going to end the day with a group of listening sessions to further inform decision making for the Committee moving forward. The listening sessions are available on our website at HRSA.gov/advisory-committees/heritable disorders. And we'll go over the questions that we're going to ask folks to address during the listening session in a little bit. Could I have the next slide?

Just to give you a preview of tomorrow, we're going to have an update on those sessions with Committee discussion. We're going to have a Phase 1 update for the Duchenne Muscular Dystrophy evidence-based review. We're going to have an update, a Phase 1 update on the Krabbe Disease expedited evidence review, and then consider any new business.

Next slide please. I did want to see if there's any discussion on the agenda, or any additional points that folks hope we cover in the next two days. Okay. Next slide please.

Oh this isn't our public comment period, so I'm going to pause for a minute.

NASEM Workshop Update: Next Generation Screening – The Promise and Perils of DNA Sequencing of Newborns

at Birth

DR. CALONGE: In previous meetings we requested an update on the National Academy's workshop on next generation screening, the promise and perils of DNA sequencing of newborns at birth. One of our organizational representatives, Natasha Bonhomme, served as the Committee Co-Chair for this one-day public workshop to examine utilization of DNA sequencing, as a supplement to traditional newborn screening for conditions that are treatable, but not clinically evident in the newborn phase.

Natasha Bonhomme serves as an organizational representative to the ACHDNC for Expecting Health and Genetic Alliance. Her focus is on centering families' perspective into policy and program design and implementation. She currently is the lead on several initiatives, including Babies First Test, which is a national newborn screening resource center, which reaches over 600,000 families and health providers annually.

Also, the Perinatal Nutrition Collaborative, a coalition of organizations and nutrition experts that share emerging science and research efforts. And then on numerous committees on maternal health and dignified care through the prenatal and postnatal periods. I hope you all join

me in welcoming Natasha Bonhomme, and we look forward to your presentation.

MS. BONHOMME: Great. Thank you so much. I want to make sure you can hear me okay?

DR. CALONGE: We can.

MS. BONHOMME: Wonderful. Well thank you so much to the Chair and the Committee for inviting me to give this recap. We can go to the next slide. Just as a bit of background on the National Academies. It was started quite some time ago with Academy's charter passing Congress, and this being signed by President Lincoln in March of 1863.

So, really just to give the sense that the National Academies has been part of the scientific dialogue in this country for well over a century. The core values are independence, objectivity, rigor, integrity, inclusivity and truth. Next slide please.

And you will notice that on a lot of my slides there is a lot of text. That really is meant to be a reference, and I will really only be selecting a couple of things to speak on from each slide, so that we have enough time in the discussion period. But on June 7th of this year, myself and Cathy Wicklund, who is actually a former voting member of this Committee, Co-Chaired this workshop. Next slide please.

The goals of the workshop was really to examine the known and expected benefits, as well as the potential harms of the widespread utilization of newborn sequencing. It was really core to the work that we were doing to explore the ethical data, security and ownership issues that are associated when you're doing DNA sequencing, but particularly, when that's happening with such a vulnerable population, such as newborns.

We also wanted to address issues of next-generation newborn screening equity in the United States, and to explore the scope of recently initiated programs that are starting to do this work. And of course, we wanted to make sure that families, patient advocates, and public health system representatives were there to be able to give a range of perspectives.

Now, the National Academies under this structure of the workshop is not meant to give recommendations. It really is meant to bring thought leaders together, and to have an active discussion. Next slide please.

These are the Committee members. I won't go through all of them, but there are many familiar names on here. And it really is through the power of this Committee that we were able to have such a

robust discussion. We had over 700 registrants for the workshop, and out of the I believe, 18 or so speakers we had, only 4 of them had ever presented at the National Academies before, and I think that really shows a testament to our desire to have a real diverse group of voices, and really new voices into this discussion. Next slide please.

So, for some background we really wanted to be able to speak about ethics and equity throughout the day, so there wasn't necessarily just one panel that was meant to focus on that, but we really pushed the different speakers and presenters to think about equity through the lens that they were looking at this issue from, whether that was from a health system perspective or a research perspective.

We also were not asking if sequencing in healthy newborns should be done per se, but really the fact that this is already being implemented, and how can we do it responsibly, and equitably moving forward. And that was something that we did go back and forth on a bit at the beginning because we wanted this to really be rooted, not just in the theory of what could happen, but really rooted in what is currently happening today. Next slide.

So this is an overview of the day. As you can see, these are all big topics. While this was

about an eight-hour session, it could have been a three week session. There is a lot to go through, but we did the best we can. And I will give kind of a mini recap on each of these sessions. Next slide please.

So we had our keynote, which was done by Dr. Aaron Goldenberg, and again, really rooting the conversation in the fact that sequencing of newborns is here. There are thousands of newborns getting screened -- sequenced in the U.S. happening today already, and when we look globally there are a number of different programs that either have launched, or are planning to launch in the next six months.

So some key considerations to start off the workshop is really what is that difference between screening and sequencing, and how are we using language to make sure that we are being both accurate, and not necessarily conflating different things?

Is there a difference in terms of healthy sequencing, so that idea of the preventative approach compared to the diagnostic, or treatment approach? So when we're thinking about whole genome sequencing, and sequencing of sick kids in the NICU. We wanted all of the presenters to be able to speak to return of results.

Are we returning everything? Some of the things? Is this happening over time? What does that mean when we are thinking about current laws, when we think of 21st century cures, which has really how they push to make sure that patients and people can get their results once they are created.

And there was the topic of uncertainty in the findings that came up quite a bit throughout the sessions, and it was really kicked off as part of the keynote. Next slide please.

Some of the proposed actions from our keynote speaker was really to look at how can we promote regulatory structures to support translation? So yes, there's a lot happening on the research side, but we really need to start planning for implementation, and what would that look like.

How to make sure that we're building strategies from the beginning to hear from parents, and I will say, the Co-Chair, I would also add into that, from people who are actually affected with these conditions, and to make sure that there are a number of different opportunities for input.

A real drive to avoid, excuse me, giving into the fact that we have an inequitable healthcare system. We know that that is the case, but that doesn't mean we shouldn't be also trying to see how

introducing new technologies and new approaches could be structured in a way to help solve, or at least move the needle in a positive direction when thinking about equity in healthcare, and establishing that culture where equity and ethics are foundational, not just something we think about at the tail end.

And of course, we really challenge people to, you know, really think about their own assumptions, to challenge the assumption that this of course would happen as part of state-based newborn screening, or to challenge the assumption that of course everyone would want whole genome sequencing for themselves or their child. And to really try to look at these issues in a more dynamic way. Next slide please.

The discussion really did go back to, even though we really tried to say to challenge your assumptions, there was a lot of discussion around state-based newborn screening programs, and the fact that they are fragile, and not to say that they aren't strong, but really we know that there is so much pressure already on that particular public health system.

And we know that follow-up care and intervention can be inconsistent and costly. That was a theme that kept coming back up. You'll see

that on multiple slides here, in terms of how do we protect current newborn screening, while also making sure there's opportunity for advancements.

There were questions about, you know, who gets to define newborn sequencing? What do we mean by it? What is it? And what it isn't. A good example of that is the idea that oh, do you really learn everything if you get a newborn sequenced? You know, making sure we're not painting a picture that isn't quite accurate, that we know sometimes with sequencing, as with any additional technology, you get more questions than answers.

And the idea of promise and perils though, a nice title, doesn't mean that we were trying to aim for a perfect balance between the two, that there still was a lot to learn. We had one of our speakers really address the fact that we have plenty of examples of introducing a technology that was meant to streamline services, and make things more equitable, and in fact, actually exacerbating that.

Some of the examples that were brought up was the use of facial recognition in law enforcement, and how that has been tied to the arrest of innocent black men, again, the implementation of a new technology actually leading to outcomes that are opposite of what it was supposed to. And we see, we

have many examples of this, and how do we make sure sequencing doesn't fall into that? Next slide please.

The discussion continued with active contributions from the different speakers around psychosocial benefits to parents and families. The idea that oftentimes families are the biggest source of support when thinking about expanded screening or sequencing options, that there really needs to be a much more robust discussion of benefits and harms of screening versus not screening.

I know that's a topic that has come up with this Committee before as well. And really the idea of if remaining in the status quo is seen as the safest option, but it is currently failing families, what we need to do about that. Next slide please.

So, then we went into Session II, where we had an update from a range of different programs that are doing research in this space, and really trying to understand the lessons learned from newborn genomic testing and screening. The programs that we highlighted are on the screen. It really delved into clinical utility and validity of sequencing.

The issues around variant interpretation were brought up, and really this idea that sequencing is not in a position to replace screening, or newborn

screening. And I will say, as a participant in the workshop, not speaking for the National Academies in any of this, but it was really clear from the programs that this was an important point to drive home during the presentations, that sequencing is meant to be an add on, an added benefit of either may be in the public health program as it stands currently, or in a clinical setting.

But that it really was not meant to be a replacement. And I know that is sometimes a theme that has come up that I thought was interesting during the day that people were really committed to. There was quite some active discussion around the hype versus reality of sequencing, and what does that mean, and how important it is to really form partnerships across all sectors, but particularly the relationships between researchers, regulators and families. Next slide please.

So, we kept the day moving, and started talking about what implementation, challenges and opportunities there were through the lens of a health system. And of course, many of the themes that we talked about on this Committee came up in that discussion as well, but particularly the issues around workforce training and education.

I think every health-related sector is

concerned about workforce, and that was no difference in this discussion. The importance of diversity in both the data that we are able to obtain and the workforce, I will say as part of the end of the day recap, I thought it was important to say though of course we are all committed to diversity in the workforce, we should not make the assumption that just because you have a more diverse workforce, you're going to solve all of your equity issues.

And one, it's not fair to put that onto populations that have been historically excluded from these roles, and so to really be thinking about the nuances between that connection of diversity in our datasets, diversity in the populations who participate in all of this work, and the diversity of the workforce.

Again, the idea of trust came up, and that we still have to build trust. I mean really in relationship building of course, are always building trust, and really need to be able to commit to that. There was some discussion about the current newborn screening system in the places where it is not an equitable system, whether you compare the range of conditions that are screened from state to state, as well as different times to follow-up around different conditions, as well as depending on the ethnic

population that a child may be a part of. And that we really need to be grappling with these issues, not only within the context of sequencing is here, or sequencing is coming, but that this is part of the system that we already have in place. Next slide please.

So, we did have a session that really looked at implementation, and what that would look like from a responsible and equitable way. And of course that discussion was really rooted in the idea of engaging with groups who really have been excluded from other scientific advancements in the past, and really having that opportunity to foster the culture of trust, equity and respect.

There was really a focus on engagement and empowerment for community buy in, and to be clear that buy in wasn't necessarily a so that every community says yes to this, but that every community can really feel that they've been part of the decision making process for themselves, and for society around how they are moving forward with the implementation of this technology.

There was a lot of discussion and examples of actually asking people directly about their needs, and what was important to them, and really accountability in terms of when there are research

projects, or new initiatives, and yet they still have gaps in outreach, education and communication, and that we really need to start calling that out in the work that is present. Next slide please.

And so we started to wrap up with the concepts of, you know, will sequencing in the newborn period change the trajectory of precision health? And really this idea that there needs to be some clear lines that really show improved health, or care as a result of any type of screening with any type of technology. And evaluation and accountability beyond just a diagnosis -- that it isn't just about being able to say how many kids we caught with a certain condition, but really a system of intervention, so we can answer the question is this child's life better because of the different parts of this system that they are now a part of?

And the importance of increasing genomic knowledge around healthcare providers in general. If genomics is really going to be integrated at this level, then all parts of the healthcare system need to be a bit more knowledgeable and have a better sense of where to get information when thinking about genomics.

Some of the remaining questions was how should genetic information from birth be used across

the lifespan? Again, this idea of will this be disruptive to traditional newborn screening models, and could sequencing be ruled out at different ages as part of routine clinical care?

We know that there are some research projects that are looking at that very question right now. And what can we do to make sure screening is more equitable? And how will all those who need follow-up care actually get it? Next slide please.

So, as you can see I've been a bit repetitive. We had some key themes that just ran throughout the day, building trust, who gets to decide what the harms and benefits are, and what the balance should be? How are families, who are both those who are affected by a different rare, or genetic conditions represented, as well as people who are part of the public, who will also be encountering these technologies. The issues around workforce are very real, and there are not many it seems, solutions out there, so really needing to build that. And the idea that we already have inequities, and how does the work that's being done around sequencing help us improve upon them, not simply build on top of them. Next slide. I think that's my last slide.

And Dr. Calonge already covered this, so if you need the links to both the description, as well

as the application for the newborn screening study that was mentioned already today, they are right here. Thank you.

Committee Discussion

DR. CALONGE: Thanks so much Natasha, that was just excellent, and it sounds like it was a very great day. And I certainly appreciate your leadership and Catherine's as well, the participation of all the workshop participants and the proceedings were quite useful, so thanks so much for that, and for the plug for membership for the upcoming consensus study.

I'd like to open up the meeting to the rest of our Committee for questions and comments, and as usual I'll start with Committee members first, and then move on to organizational representatives as time allows. And I see the first hand up is Jennifer Kwon. Jennifer?

DR. KWON: As I found my mute button I thought I would go for it. Thank you. This is Jennifer Kwon, Committee member. Among the definitions that you were talking about Natasha, do you have a definition for newborn screening? Was that discussed?

MS. BONHOMME: Are you asking do I,

Natasha, have a definition, or the workshop participants?

DR. KWON: Well I think it's an important question. I mean I think I throw it out there because I think the Committee has seen that we probably operate under somewhat divergent definitions of what newborn screening is, currently even. And I think that operationally, or having sort of a goal, like having, sort of saying what are we trying to accomplish with newborn screening today, tomorrow seems an important part of discussing the technologies of the advances that we have.

Traditionally, newborn screening has been really driven by technological advances. It was started by technological advances. But we have always had this tension of this desire to emergently diagnose and treat a certain category of childhood diseases. You had that tension between that, and then the expanding nature of the technology, and how many things we can potentially diagnose, but maybe not necessarily treat.

So, I wonder if you at least heard overarching themes of what people thought newborn screening programs should do, sort of at a minimum.

MS. BONHOMME: Great. Thank you for that elaboration. I would say there was no one in the

room who was saying what state-based newborn screening program should do because I don't think anyone in the room thought that was the purview of the workshop. And but what did come up was really when people said screening what do you mean?

Do you mean state-based newborn screening, or do you mean the screening of maybe that may happen during a clinical visit, and where sequencing should come into play? So I believe the conversation really went to trying to push people to be more specific when they said their terms, but we know that there are sequent research sequency projects that are calling themselves newborn screening, you know, or a newborn screening program, or something like that.

And so, we really as the Committee who are the planning committee, really as moderators would try to say oh, what do you mean? Do you mean state-based public health, or do you mean something else to really try to push people to be more specific with their terms?

DR. CALONGE: Thanks. Michele?

DR. CAGGANA: Thank you. Thanks Natasha, for that recap of the workshop. I was very excited to hear that it was acknowledged that these types of programs should be complimentary to traditionally newborn screening. That's one of the things that

we're trying to establish with the Guardian program that we're working on.

I was just curious what, from the perspective, you know, arranging this Committee, what's the next step here? I feel like we keep gathering to talk about the issue, and I'm thinking what's the next action step that the planning committee, or the members at the workshop felt was necessary?

MS. BONHOMME: Great. So as is the approach of the National Academies, there was a report, which I believe was in the briefing books, and that is where this discussion -- I don't want to say ends, but this work ends for the National Academies. And they really are positioned to bring up the issues, and say hey society, look what's happening.

That being said we know that there are a number of other places where this discussion is happening. Last month there was a meeting in London through the IKONS group that is discussing this at a global level, and we're talking about it here on the Committee, but I think your point is very well taken. Who is going to actually move forward, not on the discussion front, but on the action front? And what should or shouldn't we be implementing?

DR. CAGGANA: Thank you.

DR. CALONGE: Next we have Shawn McCandless.

DR. MCCANDLESS: Thank you, and just to repeat Natasha, thank for that nice summary of what sounds like a really interesting meeting. I'm a little bit confused by some of the language that's being used around sequencing, so I see the terms Next Generation, DNA sequencing. I hear the word sequencing is currently being used.

I heard you say that sequencing is currently being used, and so the discussion was focused around how to do that responsibly and equitably, rather than discussing whether it should happen. When I read the report it really seemed more focused on genomic sequencing, or exome sequencing.

And so, two questions. The first is what really -- what are we talking about? Are we talking about the use of DNA sequencing technologies in newborn screening? Or are we talking about genomic sequencing, sequencing entire genomes or exomes for the purpose of newborn screening, or to enhance newborn screening?

The second question then is really a little bit more philosophical, and that is if this group went into this with the assumption that it's already

happening, and therefore this is not -- we've already missed the boat on discussing whether genomic sequencing should happen as part of newborn screening. I would push back very hard against that conception.

We actually -- this is the time that we have to be discussing this, and all of the discussion at this meeting was around evidence that would support or not support the utility and the potential harms, the potential benefits of sequencing. This discussion we need to have now is should exome and genome sequencing be part of newborn screening.

And if we don't have that conversation now, when are we going to have it.

MS. BONHOMME: Thanks. So for your first question it is about genomic sequencing. I think what has happened is that we automatically say genomic sequencing as part of newborn screening. That is not what the whole session was about. It was about genomic sequencing during the newborn period. That could be state-based newborn screening, but it doesn't have to be, and that's really where that discussion of challenging our assumptions really came in at the beginning.

So I completely agree with you that there does need to be a discussion, and there continues to

be a discussion about genomic sequencing as part of state-based, mandated newborn screening. So that was not what was said in terms of the ship has sailed on that. The ship has sailed, or I don't know if that's like even the right metaphor.

But on the fact that today, as part of research projects, there are newborns getting sequenced. Like that is a reality, and to not have the discussion as though it is something that's going to be far away, which I think in previous years we have, right? This idea, like that's where we're going, that's where we're going.

And the purpose of the workshop was not to be rooted in we are going to a place where newborns will have the opportunity, or be presented -- families will be presented with the choice of having their newborns receive genomic, newborn sequencing in some capacity, but that there are families facing that today, even if they are part of a research project.

Just because it's part of a research project doesn't mean it isn't the reality of that family. It is the reality. That is what they're being offered, and they're making a choice whether to opt into that or not. So does that clarify, you know, the distinction that we were trying to make in

the workshop? It wasn't to say oh, we shouldn't talk about it, but I think there's just an assumption that oh, we must be talking about it within state-based traditional newborn screening, and that's where there's still plenty of conversation.

But we wanted to acknowledge that every day there are families in the U.S. and in other parts of the world that are being given this option to have genomic sequencing on their newborns.

DR. MCCANDLESS: That's certainly true, and not just as part of newborn screening, but mostly as part of clinical care. That's where the bulk of genomic sequencing is occurring right now, and hopefully we can learn a lot from that. I would just like to ask all of us, and to become evangelists, if you will, for correct usage of terminology because this conflation of DNA sequencing with genomic sequencing is very problematic.

It's problematic even within professional communities, and people who think about these things every day. And so, I would just encourage us to be really precise in our language. When we mean genomic sequencing, say genomic sequencing. Let's not use sequencing as a shortcut for genomic sequencing because it's confusing. And it will be very confusing to patients and families and the public as

these discussions become more broad, so we need to be -- I just think we need to be really careful.

MS. BONHOMME: I completely agree with you. I think for those who've known me a long time, I'm always asking and saying how important language is, and I think it would be great have our professional societies really be in alignment, and agreement around language, so that then there's a standard to point to. I completely agree with that.

DR. CALONGE: And Jeff --

DR. BROSCO: Shawn, can I just jump in for a second? Can you tell us the difference between genomic sequencing and DNA sequencing, so we're all on the same page for those that don't do this every day?

DR. MCCANDLESS: Sure. So DNA sequencing is essentially determining the sequence of any piece of DNA. It could be as small as a few base pairs to as much as an entire genome. In general in the past, sequencing has generally referred to a gene, a single gene, and usually just the exons of that gene.

And so in genomic sequencing, that term is a somewhat generic term that usually means that you're sequencing as all of the genes are essentially all of the genes as the same time. It comes in two flavors. There's the exome, which is only sequencing

the parts of the DNA that are the instruction for how to make a protein, or what's referred to as the coding region, which is the exons of the genes, and so it's the exome.

Or the whole genome, which is sequencing essentially all of the DNA, or most of the DNA. The term genomic -- so we use exome for the coding region. Whole genome for sequencing the entire genome, and then the term genomic sequencing is often used in the field as a placeholder for both exome, or whole genome, implying that you're sequencing all the genes at some depth at the same time.

And then if I might just say panels usually refer to sequencing multiple genes that are associated with a particular clinical problem, and then there's single gene sequencing. At the end there's also, and not to belabor the point, but the term that is often not used, but should be is genotyping, and genotyping is where you look at for specific variants in the population.

So, if you do 23 and Me, they don't sequence your entire genome, they look at hundreds of thousands of variants of base changes that are common in the population that allow you to say something about the genome, but it's different from sequencing, and so genotyping is a separate technology.

Sorry, that was probably a lot more than you wanted.

DR. CALONGE: Ash?

DR. LAL: Great. Because Shawn's comments are certainly useful for the comment that I was going to make, is another type of -- so the workshop of what the NGS, and I think another one that was mentioned briefly within the proceedings is targeted NGS. So, and I wonder even though the workshop took the whole of view considering the entire issue surrounding the use of NGS, but are there situations within the diseases that we are attempting to screen for where you're more ready to use targeted NGS.

And from that, I mean that we are actually looking more closely at some particular genes, and not trying to do either a whole exome or a whole genome sequence. And the argument against that is what we mean that all the markets on this end, ethnicity-based differences in some of the changes in the DNA sequence are not fully worked out, and it leads to uncertainty.

So, but that's a general comment, and I would hope that there may be specific conditions that are more ready for considering the targeted NGS. And as an example, I would just put forward the gene that I'm assuming it is the globin gene, so that I wanted

to ask Natasha, especially if there's a room where the use of NGS could be applied for specific conditions to either compliment or maybe even to replace the current matter of screening.

MS. BONHOMME: Yes. So from the workshop perspective, they did not go into that type of detail. It really was at a more 30,000 foot, but I think that maybe is a type of question that would be useful in this Committee that looks at more implementation, particularly within the public health system, not to tell this Committee what to do.

But maybe that the expertise around the table here, the virtual table here, would be able to really dig into some of those things you brought up.

DR. CALONGE: I'm going to let us run over for a few more questions, maybe about five minutes, and then I'll just assure our people signed up for public comment that we will also allot over five minutes the other way, to make sure we have time for public comment, but with that comment, make sure we keep our comments and questions short, and Steven Ralston, you're next.

DR. RALSTON: All right. Thanks very much. I'm the representative from the American College of OBGYN, and I just wanted to thank Dr. McCandless for his comments and his primer on genetics, but I can't

agree more wholeheartedly on implementing this now, or even thinking about this implementing now. It's just not possible because we don't have the infrastructure in place to deal with the results.

We don't have all the genetic counselors that we need just for regular newborn screening, I think, let alone any kind of whole exome sequencing that we might be doing. And that the burden of the beginnings of this counseling is going to fall on OBGYNs because we are the ones that start talking to patients about newborn screening, and we are just not equipped to talk about this kind of genomic screening in the newborn period.

So yes, we'll use it clinically for prenatal diagnosis, et cetera, and that's fine, and we're good, but that's rare in obstetrics. That's all I wanted to say, thank you.

DR. CALONGE: Thanks. Jannine Cody?

DR. CODY: Yeah. Thank you, Natasha, and Shawn for helping me think about this a little more clearly. And I appreciate that the National Academies had a very, very broad take on this issue. But I think for our Committee, our question really is in let's see, what are the requirements we would need in order to have full genome sequences pre-symptomatically on newborns as a state program?

Okay. Before everybody melts down, okay, I realize that's 10,000 years or whatever, a long ways away, but if we start with that as the end, then we need to work down and say that are all the things that need to happen. I mean as was just mentioned, workforce is huge. Maybe we parse that out and say specific conditions, or certain criteria. But I think it all comes down to the definition, and that's what we're really all about is state-based newborn screening. And so, I think we have to start with that, and then start listing, okay, here's all the things that need to happen, diversity, inclusion and workforce, and cost and all those things have to come into it.

But I fear that we may be starting down, picking out this case versus that case, and really what's fundamentally different about full genome sequencing is that it's the whole genome. And so, I think we have to start there, and then as I don't know want to say it's a goal, because it might not really be the goal.

But it's sort of the ultimate, and then work back. Does that make sense?

MS. BONHOMME: Can I just jump in here? Again, I want to make very clear I'm not a representative of the National Academy, as I make

this statement, but I do think considering that this Committee's title is Heritable Disorders in Newborns and Children, I don't know if that means it's only state-based newborn screening, so I don't know that, and I'm not in a position to make that distinction, but I think just you saying that may be something too, at some point this Committee may want to talk about or not.

DR. CALONGE: Thanks again, Natasha. I wanted to tell Cindy Powell, Susan Tanksley and Michele Caggana that we're -- if you could write your comments or questions down, and send them in. If we have another point in the agenda, we'll try to get back to those, but I don't want to short-change our public comment period, and I want us to all give our profound thanks as usual to Natasha for a great presentation and Q and A, and I know you'll have comments later as we move through the rest of the agenda.

Public Comment

DR. CALONGE: With that, I'd like to turn to the public comment period. We received two written comments provided to the Committee in advance of the meeting. These were from the EveryLife Foundation. One was Pioneering the New Era of

Newborn Screening, collaborative insights and recommendation for modernizing NBS systems, and a full study report on the cost of delayed diagnosis in rare diseases, a health economics study.

We're also fortunate to have requests from 20 individuals to provide oral comments. Due to the number of public commenters, we're requesting that commenters adhere to the time allotted of two minutes per commenter, and I will call you in the order that I have, and we'll move forward right away with Annie Kennedy, if you could unmute please. Annie, are you with us? Yeah, we'll come back at the end and try again. So I'm going to move on to Dylan Simon.

MS. KENNEDY: Yep. I'm here. Sorry. I didn't get promoted as a panelist.

DR. CALONGE: I'm sorry.

MS. KENNEDY: Nope, that's okay. Hi. I'm Annie. I'm with the EveryLife Foundation for Rare Diseases, and I serve as our Chief of Policy Advocacy and patient engagement, and that's wonderful to be with you all here today. As you know, the EveryLife Foundation for Rare Diseases is an evidence-based policy organization, and in 2022 we published a National Economic Burden of Rare Disease study that at that time found that the economic impact of rare diseases in the U.S. was nearly a trillion dollars.

And really importantly in that study what we found was that 60 percent of those costs were costs that are shouldered directly by families and society. And about 40 percent of those costs were the direct costs. But another finding in that study was that we found that of the survey respondents who helped us to ascertain the indirect and non-medical costs in the study, the diagnostic odyssey was nearly 6.3 years, and included about 17 medical visits.

So, as all who are gathered here today understand, timely diagnoses enabled through newborn screening, can eliminate that diagnostic odyssey, resulting in prompt life-saving treatment of disease. So what those findings led us to want to better understand, was whether we could quantify those cost savings of eliminating the diagnostic odyssey and what that yields for families, including time spent managing financials, time off work for healthcare visits, and in many cases the out of state trips associated with diagnostic -- that diagnostic odyssey and managing a rare disease. So guided by an expert advisory committee, the EveryLife Foundation worked with the Lewin Group to conduct the cost of delay diagnosis in rare disease, a health economic study, which we submitted to you prior to this meeting.

We assessed seven rare diseases, five of

which were pediatric onset diseases, three of which are on the RUSP. In ALD, Pompe and SCID, where routine newborn screening has been implemented in some or all states, we found that timely diagnosis not only can eliminate the diagnostic odyssey and its associated medical costs prior to diagnosis, and provide the opportunity for optimal intervention and improved health outcomes, but we were able to show what some of those health economic benefits are.

I'm going to highlight, just for the sake of time, some of those avoidable costs attributable to delayed diagnosis work. For Pompe, we found that the avoidable costs attributable to delayed diagnosis were $168,700.00. For ALD $300,600.00. And for SCID $517,000.00.

We also considered the avoidable pre-diagnosis costs for two additional pediatric onset conditions that are not yet on the RUSP, and found them to be for Fragile X, $94,200.00 and for Duchenne Muscular Dystrophy, $94,900.00. This was a conservative estimate of productivity loss, and did not include the account of travel time, which can be substantial in rare disease.

We highlight this today because it's incredibly apropos for our discussion later today on how we quantify costs, include them in our

evidence-based considerations. We highlight that while medical costs are unavoidable in rare disease, the avoidable costs attributable to delayed diagnosis represent the burden on patients and families searching for a diagnosis, and delayed diagnosis also prevents healthcare dollars from being spent on treatment and supportive therapies that improve patient quality of life, and may even increase workforce productivity.

So, our recent study yet again underscores the incredible and critical importance of the work of this Committee.

DR. CALONGE: Please wrap up, please Annie, thank you.

MS. KENNEDY: I'm just going to say thank you for your efforts, and we look forward to further discussions on how we can continue to collect this evidence-based data, and integrate it into our newborn screening system. Thank you.

DR. CALONGE: I want to remind people to try to stick to the two minutes. Annie was well over that, and hopefully we can get back online, back on time, and thank you for your comments, Annie, now we're on Dylan Simon.

MR. SIMON: Good morning. Thank you for the opportunity to speak to you today about the

written comment that we had submitted earlier as well, around the modernization of newborn screening. So we brought together a group of newborn screening stakeholders from across the newborn screening community, including patient advocacy organizations, lab directors, trinity, to hold together a newborn treating model.

This roundtable to address not only challenges that are currently facing newborn screening, but to address the challenges that will emerge as innovation, and during development and testing continue to progress in the coming decades. And so when we develop those series of roundtables we aim to develop actual policy solutions that can make improvements now into the future of newborn screening.

And as I said, we want to make sure that we had a diverse perspective on those issues, so we made sure to include patient advocacy organizations, state lab directors, academic researchers, industry, as well as physician representatives, to ensure the fact that we're including as many perspectives as possible. Because when we were developing these solutions we wanted to make sure suggestions were grounded in what was possible.

And so, coming out of that roundtable we

had four key themes really identified, and in terms of how to organize those solutions. And so the first theme was increasing federal leadership and accountability and transparency within federal newborn screening programs, so there are multiple solutions discussed within that process. But among them was the idea of how do we ensure the fact that the patient perspective is better included within the ACHDNC review process.

The second theme looked at regional lab networks, and specifically talking about how to establish the regional lab network that provides state newborn screening programs with the opportunity to work together, and to ensure efficient and faster addition of newborn screening conditions.

And solutions here really center on the idea of how do we ensure federal leadership in determining how best to create these new labs, and how they'll work with the states. We do see these kind of regional lab networks already exist, whether it's in Massachusetts screening for multiple states, Iowa, or other states of that sort.

But if we're going to create kind of a federal regional network, we need to ensure the fact that there is federal leadership that is going to work with the states doing what works best across the

country. Theme three really looked at --

DR. CALONGE: You're at two minutes now, Dylan, please wrap up.

MR. SIMON: So the third theme really looked at how to increase access to publishing data, so really moving forward how to support the ED3N Project. And the fourth theme really looked at how to integrate Next Generation sequencing in a proper manner. And I know we've talked a lot about that this morning, so I'll move past that.

But really at the core of that is an understanding that there have been a lot of changes within newborn screening, and the world around it in the last 20 years, and to truly modernize newborn screening system, a multi-faceted approach is required across the country to improve the entire system. Thank you, and I'll pass it back.

DR. CALONGE: Thank you, Dylan, for your comments. I'd like to move on to Marianna Raia.

MS. RAIA: Thank you. Can you hear me?

DR. CALONGE: Yes.

MS. RAIA: Thank you, Dr. Calonge, and thank you to the Committee for the opportunity to share with you today three key updates related to our newborn screening education and engagement initiatives. My name is Marianna Raia, and I have

the privilege of working as the Associate Director of Programs at Expecting Health.

Our programs are driven by clear vision that the fear and confusion individuals and families face during pregnancy and parenting is replaced by confidence and agency to make the best healthcare decisions for their lives. We do this through a number of different programs.

The newborn screening family education program was a HRSA funded program, which just concluded on August 31st, and has been dedicated to developing opportunities for all families to learn about newborn screening. We've developed creative training and educational resources to build competence for families to become leaders in the newborn screening system, and now is the time to invite these families to your tables.

To date, over 6,000 families have been trained and educated through a combination of efforts, including online training and education modules, online video education, and targeted initiatives to raise awareness and knowledge of newborn screening during the prenatal period.

Additionally, the program has developed an extensive partnership network of 62 organizational and individual partnership relationships which are

integral to the dissemination and connection to families. 22 family leaders were trained, and over 18,000 individuals for medically underserved communities were reached.

The success of this program is based on the pillars of extensive system knowledge, strong partnership community trust, and practical resources that meet families where they are before, during and after newborn screening. Unfortunately, funding for this program concluded in August, leaving a gap in the engagement of families as partners in the newborn screening system.

In addition to the work that we've done through the newborn screening family education program, we've also supported the newborn screening community through many other programs and partnerships. In 2021, Babies First Test established the first of its kind GRACE award, which stands for generating real action by cultivating engagement.

And to date we've awarded four groups, including the Illinois Sound Beginnings, the Connecticut Newborn Screening, excuse me, the Connecticut Newborn Diagnosis and Treatment Network Screening Class, and our most recent 2023 award winner SCID Compass.

Each of these groups is recognized for --

DR. CALONGE: We're at two minutes now, thank you.

MS. RAIA: -- families, communities with grace, strength and innovation to generate action in the newborn screening. So as this Committee knows well, newborn screening is more than just a screening at birth, and we believe that families are integral to driving system change, and supporting positive family experience with the newborn screening system.

And thank you for your time today. We thank our partners at HRSA for the opportunity to build the framework, and we urge you to consider ways to ensure that families are not participating just as recipients of the screen, but as active, engaged partners in their work. Thank you.

DR. CALONGE: Thank you for your comments, and the work. I'd like to move on to Omer Abdul Hamid.

DR. ABDUL HAMID: Hello. Thank you for the opportunity to speak with you today. My name is Omer Abdul Hamid, and I'm a neurologist at Nemours Children's Hospital in Central Florida, and the Director of the Neuromuscular Program, where we see around 100 families with dystrophinopathies, and I'm here today to advocate for the inclusion of Duchenne on the recommended uniform screening panel to approve

access to treatment.

I'd like to share two contrasting stories, which highlight how early diagnosis affects access to treatment. The first story is of a patient who we recently diagnosed with DMD in our clinic a few weeks ago. His family began to notice differences between him and his peers at age 3, and when they took him to the pediatrician, he was labeled as a late bloomer, and they were told that he would catch up with his peers over time.

His parents, while concerned, trusted their pediatrician and enrolled him in physical therapy, but he continued to get weaker and weaker. Shortly after his sixth birthday, routine lab work showed that his liver enzymes were elevated, and the pediatrician told the family that he likely had liver cancer, and referred them to a gastroenterologist, who checked the CK and it was elevated to 2,000 -- 20,000, pardon me.

He was then referred to our clinic at which time a diagnosis was established. What was more devastating than learning of the diagnosis, was learning that because he had just turned six, he was no longer eligible for the gene transfer therapy that was recently approved. Had he been diagnosed with DMD earlier, he would not have been deprived of this

opportunity for a life changing therapy.

Contrast this with two brothers that we had treated in our clinic with exon skipping in infancy, who were identified prenatally. These brothers are doing very well, and meeting milestones on time, and improving on their outcome measures more than what would be expected from the natural history. Their mother is very grateful that they were able to access treatment before it was too late.

Unfortunately, many patients are getting -- still getting liver biopsies for these elevated liver enzymes before being diagnosed. While there has been a tremendous effort to educate pediatricians about DMD at the national and local level with meetings and such, the average age of diagnosis nationwide has not changed.

Thus, newborn screening for DMD is the only way to ensure that all boys with DMD are diagnosed early, and have access to these life altering treatments, which we have seen makes a big difference when treated early. I believe the benefits of adding DMD to the RUSP would ensure access to the treatment, improves outcomes in my experience, and I thank you for your ongoing consideration for Duchenne newborn screening.

DR. CALONGE: Thank you, Dr. Hamid, and

appreciate your comments. At this point I'd like to move on to Niki Armstrong.

MS. ARMSTRONG: Good morning. On behalf of Parent Project Muscular Dystrophy and the Duchenne patient community, thank you for the opportunity to speak today. I am the newborn screening program manager for PPMD. There has been continued positive progress in Duchenne, with the approval of an additional therapy, Agamree. Agamree is a dissociative steroid approved for ages two and up with an improved side effect profile.

It is important to understand that optimal treatment for Duchenne is multi-pronged, it won't be a single therapy. Treatment needs to start early before significant muscle replacement by fat and fibrosis. Duchenne now has a total of 7 FDA approved Duchenne specific therapies, an incredible pipeline of many more potential therapies down the line.

For PPMD, newborn diagnosis and subsequent treatment is personal, it's about the people. But we also understand that money makes the world go round. Consequently, we were thrilled to partner with EveryLife, to understand the costs of delayed diagnosis in Duchenne.

As already stated, the full details of the analysis were submitted as a written comment, but I

did want to highlight findings relative to Duchenne. The study used real world data to examine healthcare utilization and impacts on parental productivity relative to the pending of diagnosis.

Children were defined to have a timely diagnosis of Duchenne if they were diagnosed before age 5, given the average age of diagnosis of 5. Those with a timely diagnosis had lower annualized per patient medical costs attributed to Duchenne, and the year before, the year of and the year post diagnosis.

It cost less to get to a diagnosis, and more importantly, to care for children after diagnosis in the timely diagnosis group. The late diagnosis dramatically increased costs to families. With delayed diagnosis, Duchenne families experiencing total medical costs and productivity loss for the family of more than $211,000.00. That is a huge cost to families, to the healthcare system, and to society.

Newborn screening for Duchenne benefits babies, their families, the greater healthcare system and society.

DR. CALONGE: Two minutes.

MS. ARMSTRONG: We greatly appreciate the opportunity for Duchenne to be discussed again

tomorrow, and appreciate the efforts of this Committee, and technical group to understand Duchenne. Thank you.

DR. CALONGE: Thanks so much. Thank you. Next we have Susan Huang and William Yu.

MS. HUANG: Hi everybody. Thank you for this opportunity to let us tell you a little bit about our family. We are a New York based family to two boys, Oliver and Benjamin. Oliver was diagnosed with Duchenne Muscular Dystrophy in July of this year at age 7. He recently turned 8 years old in October.

You know, how did we even come to this. You know, this is a picture of Oliver we'll share here. This is who is he today, but at a very early age we had noticed that there was developmental delays, hypotonia, ASC ADHD, and for many years we treated the downstream impacts of Duchenne Muscular Dystrophy without understanding what was the underlying cause behind it.

And through a medical friend who happened to notice some of the symptoms of DMD, alerted us to the possibility, which then pursued -- which resulted in us pursuing a medical diagnosis, and confirming that in July. So, you know, I think about the time that we spent from, you know, less than a year old when we noticed this to the actual diagnosis of the

disease, and at age, you know 7 and change, you know, what were the impacts to our family.

You know, I think on obviously from an emotional side the DMD impacted, you know, and many of the other speakers before us highlighted, you know, the impact of a delayed diagnosis, missing out on medications, therapies, you know, clinical trial, et cetera.

You know, that's obviously very devastating for our family because doors are being shut before we even have an opportunity to open them. When we think about the economic impacts to our family, the time and money. Managing the care of a child with special needs is incredibly expensive.

I think about the seven and a half years that we spent on therapies, managing his care, insurance, et cetera. You say conservatively 15 hours a week, 52 weeks times seven and a half years, that's nearly 250 human days spent trying to manage his care before actually understanding what was the underlying cause behind this disease.

That's devastating to us, and from a monetary standpoint, we assume $34.00 per hour, which is the average wage, you know, in the U.S., that translates to roughly 200K. And so, you know, I think that is kind of in and of itself, you know,

pretty devastating, but I think there is you know, something perhaps a little bit more, you know, devastating at hand here.

You know, when we finally got the diagnosis, you know, it comes after years of being dismissed. Not being taken seriously. That's a problem. We focus, you know, feeling the medical community, you're just failing us, and this loss of confidence that society can look after the most vulnerable, like that's a big problem.

And so, today we look forward. We look forward to having Duchenne hopefully be a part of the newborn screen. On October 25th, New York State actually added newborn screening for Duchenne. It's bittersweet for us, but we're really thankful for the attention to this very serious disease. I think had we known earlier, we would definitely focus on, you know, what therapies would support him, preserve his muscles, not damage them.

When I think about home school modifications, how do we support him? We want to think about how do we partner with organizations like PPMD to support our families, and then also think a lot about family planning, like that probably would have changed how we would have, you know, where we would have settled down, whether we would have had

more kids or not.

And you know, I think most importantly, it would have really supported Oliver at a much earlier age. So you know, we can't go back in time. We can only move forward, and you know, we're really thankful for the opportunity to share a little bit about our story here, and really hope that you consider Duchenne as part of the newborn screening. Thank you. I hope that was two minutes.

DR. CALONGE: Okay. I gave you a little extra since there were two of you. Thank you. So and thank you both for being with us. If we could turn now to Paul Melmeyer.

MR. MELMEYER: 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, Vice President of Public Policy and Advocacy at the Muscular Dystrophy Association. And we're proud to serve the Duchenne, SMA and Pompe communities, along with many other rare neuromuscular disease communities.

First and foremost, we're very grateful for the Committee's vote to move Duchenne -- the Duchenne nomination onto full evidence review at the August meeting. We hope a unanimous vote is at the very

least evidence that our nomination deserves a full evaluation, and hope this is a key step in Duchenne soon joining the RUSP.

We're grateful for the time and effort expended by the nominations and prioritization work group, as it thoroughly reviewed our nomination, and came to the conclusion that Duchenne should indeed move forward to full evidence review. We agreed with comments that pointed out that the current delay in clinical diagnosis hinders collection of treatment effectiveness data in earlier diagnosed individuals, but available evidence clearly points to earlier effectiveness, and a combination of ongoing clinical trials and implementation of newborn screening, will fill any potential evidence gaps.

We agree with comments that states should be well prepared to create their own validation processes and cut-off for CK-MM testing, just as states have done for many newborn screens currently universally included on state panels. We encourage this Committee to empower and encourage states to create their own cutoffs in validating assays as this is something states in their programs are familiar with, and capable to handle themselves.

As discussed in August, efforts to accelerate clinical diagnosis, and there have been

many, have simply been unsuccessful, even when symptoms present at an earlier timeframe. While improvements could be made around the edges, newborn screening, in particular, is uniquely capable of providing an earlier diagnosis.

Finally, we appreciate comments acknowledging the importance of new therapies coming to market, most notably Elevidys, a gene therapy for boys with Duchenne ages 4 and 5. Furthermore, we strongly wish to re-emphasize comments noting the importance of an earlier diagnosis on life and family planning, PTs, speech therapy options, and much more. Thank you again for the opportunity to comment today, we look forward to the Committee's ongoing review.

DR. CALONGE: Thank you, Paul. Next up is Nathan Plasman.

MR. PLASMAN: Good morning, Advisory Committee members and fellow Americans. Greetings from Lombard, Illinois, 15 miles straight west of Chicago, downtown Chicago. As stated, my name is Nate. I'm 44 years old. Can you see me? Is the video coming through?

DR. CALONGE: No.

MR. PLASMAN: No? Okay.

DR. CALONGE: We can hear you okay though.

MR. PLASMAN: That's probably more

important. All right, there we go. I'm 44. I live with my wife, Sarah, we've been married for 19 years, and we have three children. Grace is 14, Jackson is 11 and a half, and Andrew is age 9, and he's in third grade.

I'm here today, here's a picture of our family. You probably can't see it, but I'm here today to talk about Andrew. Andrew was born on July 1, 2014. He was a handsome, healthy, happy infant. Around his first birthday Sarah began to notice that Andrew wasn't as strong, or as sturdy as his two older siblings. He seemed floppy when we would place him in his car seat, and he never crawled.

At 18 months Andrew was enrolled in an early intervention programming through the State of Illinois, so we had in home physical therapy, speech therapy and occupational therapy, and the three therapies did produce some marginal improvement over the course of three to six months.

At Andrew's two-year checkup on Friday, July 1, 2016, which was also his second birthday, Sarah voiced our concerns to our pediatrician, and because of Sarah's insistence, a blood draw was administered. We celebrated Andrew's second birthday later that afternoon and evening.

The next day, Saturday, July 2nd, 2016

around 2:00 p.m. that afternoon the pediatrician called. Sarah said Nate, why is the pediatrician calling on a Saturday afternoon of a long holiday weekend? I said honey, take the call. Well, we learned that Andrew's blood draw results had come in, and his CK or creatine kinase had a reading at 24,000.

Because Sarah had done all the due diligence, she knew exactly what it meant. Andrew was diagnosed with Duchenne Muscular Dystrophy on the day after his second birthday. Getting this diagnosis was heartbreaking, but receiving a DMD diagnosis so early was a huge blessing for our family. Why? Because the average age of diagnosis currently is age 5.

So, as a result of getting Andrew's diagnosis we rolled up our sleeves, we started researching, networking, planning. We had to recalibrate our expectations for what we thought our life was going to be. By leveraging our communities and connections, people like Annie Kennedy and Niki from Parent Project Muscular Dystrophy, we found hope, and we were told by numerous people that if there were ever a time to get a DMD diagnosis, that time is today.

There is hope on the horizon, and things

are changing. Andrew was selected to participate in a groundbreaking gene therapy clinical trial at Nationwide Children's Hospital in Columbus, Ohio, beginning in January 2019. He was dosed on January 11, 2019, and he was age 4.5. We're nearly five years to the anniversary of his dosing, and thus far gene therapy has arrested the progression of this cruel, devastating progressive muscle wasting condition.

Andrew functions like a relatively normal third grade boy. He loves recess. He loves to play with his older brother. Don't get me wrong, he doesn't race to the soccer field or the basketball court. When he's on it --

DR. CALONGE: We're going to need to wrap up if you can.

MR. PASMAN: Yeah. Andrew's trajectory for his life is drastically different because he was diagnosed at such a young age. I urge you to include Duchenne Muscular Dystrophy on the newborn screening panel. Thank you for this opportunity, and thank you for listening.

DR. CALONGE: Nate, thanks so much for your presentation. We appreciate your comments. If we could move on to Heather Arizmendi?

MS. ARIZMENDI: Hello? Can you hear me?

DR. CALONGE: We can.

MS. ARIZMENDI: Hello. My name is Heather Arizmendi, and I'm from Merrillville, Indiana. I am here to speak for my daughter, who was not given a chance to have her own voice. I am one very blessed mama of three children, all affected by the terrible disease Krabbe. My oldest daughter Evelyn was born September 6th, 2014, and was the happiest, baby I had ever seen.

At about five months she was no longer happy. She was losing all her abilities, including her smile, and was inconsolable. After months of being misdiagnosed, when she was 14 months old we learned that Evelyn had Krabbe disease, and that our perfect baby only had months left to live.

Shortly after her diagnosis we learned that I was pregnant with my second daughter. In 2017, our home state of Indiana did not test for Krabbe at birth. We had to fight to get our Molly a test, and weeks after she was born, we learned that she was a carrier for the disease. My girls only had three months together before Eve passed on April 16th, 2018.

They deserved more time together than that. On May 3rd, 2019, Owen joined our family. Once again, we had to beg for a test. Then May 10th, I

heard those all too familiar words, Owen had Krabbe disease. To put it lightly, we felt devastated. Luckily for us, we live 45 minutes from Chicago, and within an hour receiving the results, Children's Hospital and transport team were on their way to come get our baby boy, and start his -- the saving process of a stem cell transplant.

We met with the amazing team of doctors and specialists, all laying out the pros and cons of this process. The choice was a no brainer. We know first-hand what this disease can do to a child, and to a family. To decide between a few years of watching another one of my children suffer daily, not being able to talk, move, eat, and live life, like every child deserves, or choose an actual life for him.

Our choice was a resounding yes. The journey through the transplant was definitely not an easy one. We lived in that hospital for six months praying for the best, and guess what? We did receive the best. Owen, our sweet baby boy, is now the happiest, goofiest, four-year-old ever. He is literally crushing life.

Not only can he walk, he runs. Not only can he talk, he sings. Not only can he eat without a G tube, he is insatiable. He is in a preschool in a

mainstream school, can count to 20, knows his ABC's. He brings joy and laughter to our entire family.

He would not have had a chance to do any of this without being tested for Krabbe at birth, without the life-changing gift of the transplant. Isn't this something we all want? To witness a child get to be a child without needless suffering? To give what every baby born a real chance at life, to give them a voice, to help future moms and dads not have to feel the weight of knowing they will lose their child, and watch their child progressively get worse and die, without even having the chance to save them.

Every child deserves to live. Every child deserves a voice. Newborn screening works. Transplants save lives. If I were presented with watching another one of my children suffer through a medically complex life cut short, or choose life, obviously we choose lives. Thank you.

DR. CALONGE: Thank you Heather. I'd like to move on to Sarai Taylor.

MS. TAYLOR: Hi. My read time is right at two minutes, I promise, scout's honor. My name is Sarai Taylor, my daughter, Anna Taylor, had Krabbe Leukodystrophy. Anna passed away on April 2nd, 2015, at 23 months old. This is her right here.

Because of the toll Krabbe took on our daughter, the majority of her short life was spent with the inability to speak, eat, see or move. We did our best to engage with her, and give her the best quality of life we could, though she remained like a living doll until her passing.

Because Anna was not screened at birth, any possible treatment to halt the progression of this awful disease was not afforded to her. Newborns in Kentucky, no longer need to face that same fate, however. Just one day before Anna's passing, the Anna Clara Taylor Act was ceremoniously signed into law. This law enacted the standard that all newborns in Kentucky would receive Krabbe Leukodystrophy screening at birth.

Because of the opportunity given to Kentucky babies, the children that have received a positive strain and treatment are given the quality of life, or the opportunity for the quality of life that Anna never received. The affected and treated children like Tai and Malen, are able to laugh, smile, engage with others, walk, propel their wheelchairs, go to school and have an existence outside of themselves.

That quality of life should be the minimum standard for every child affected by Krabbe. Because

Kentucky passed the Anna Clara Taylor law, they started an important and necessary partnership with the Mayo Clinic, to ensure the validity of our state's newborn screening panel for Krabbe.

Mayo's panel for Krabbe is now seen as the gold standard nationwide, with zero false positives experienced since its implementation in 2016. A low-cost screen with such an impact on care should be an obvious choice. I can only image what Anna's life would have looked like if she were given the opportunity for treatment.

Would she have loved school? Would she have demanded to go see Taylor Swift in concert? Would she have used a walker, or a wheelchair to get around, or would she have needed neither? Though we will never know how newborn screening could have changed Anna's life specifically, we know better now. No child should exist as a living doll because of the state they were born in.

My family is expecting this Committee to confirm Krabbe disease as a recommended screening for the RUSP.

DR. CALONGE: Thank you, Sarai. Next I have Tara Casey. Is Tara Casey able to join us?

MS. CASEY: Yes. I'm here.

DR. CALONGE: Thank you.

MS. CASEY: Hi. My name is Tara Casey. Proud mom to daughter Caroline Cece Casey. From the time Cece was just 11 months old we started searching for why she couldn't walk on her own. We took her to every doctor, even traveling to other hospitals, but all came back with the same answer. She's fine, give her some time and she would eventually walk on her own.

However, my sweet girl was continuing to lose more abilities. Her five year old sister would have to hold her in the bathtub because she was too weak to sit up on her own, and the once soothing bath water was now making her scream and cry in pain. But again, despite MRIs, nerve conduction testing, and too many to count blood draws, doctors could not find anything wrong.

Eventually at the age of two and a half years old Cece was diagnosed with MLD, Metachromatic Leukodystrophy. We were devastated and heartbroken, but we had a diagnosis, so now we thought all we have to do is find the right doctor and treatment to fix it. That hope was soon crushed as we started to talk to doctors across the U.S. and even in Milan.

However, the responses were the same. I'm sorry. There's nothing we can do to save your two and half year-old daughter's life. It's too late.

Within three months of being diagnosed with MLD, she lost all abilities to talk, move her body, swallow, seizures began.

Cece needed 24-hour care, machines and medicine to do everything, eventually hospice. Cece courageously fought this disease while being tortured by it. Nearly four months ago, on July 10th, Cece took her last breath, with her amazing nurse, her mommy, daddy and 13-year-old sister lying in bed with her.

My daughter was so beautiful, and made such an impact on everyone who met her, but she also broke a lot of hearts, of those that loved her so dearly as they watched her suffer every minute of her ten short years of life. This is not okay. Newborn screening would have saved her life, and gave her options for a better quality of life.

Now is the time to make it okay, to make a change. Newborn screening couldn't save my daughter, but it will save another daughter, and another sister. We know that four families were recently diagnosed from newborn screening in the EU, and those families will never have to stand here knowing this pain. Thank you.

DR. CALONGE: Thank you so much Tara. I'd now like to call on Maria Kefalas. Maria, can you

join us? Are you on -- there you are. Yeah, I think you're on mute.

MS. KEFALAS: Or I'm having some technical difficulties with my internet, can I have someone else go while I resolve them please?

DR. CALONGE: Of course.

MS. KEFALAS: Thank you.

DR. CALONGE: And I'll come back to you, Maria.

MS. KEFALAS: Thank you.

DR. CALONGE: Let me move on to Kendra Riley.

MS. RILEY: Good morning. Do you see me okay? There we go.

DR. CALONGE: We can.

MS. RILEY: All right. Good morning everyone. My name is Kendra Riley. I'm from Phoenix, Arizona, where I live with my husband and our three daughters, and run my small business. I'm here today with one of my daughters, Libby. You can see her in the background because two of our three children were diagnosed with Metachromatic Leukodystrophy, or MLD, in 2020, at the height of the global pandemic.

Libby, as you can see, she is age 5, and she is now in hospice. While our other daughter has

zero symptoms, and is living a life of a happy, healthy three-year-old. Without newborn screening this will be the outcome for any family who faces an MLD diagnosis in the future.

They will be forced to sacrifice one child in order to save another. Our daughter Libby here, her only options as a symptomatic child, was a clinical trial to hopefully stall the disease, which failed miserably, and caused further surgeries. It only took 90 days after her diagnosis to lose her ability to walk, then talk, and then eat on her own.

She now takes 9 medications a day to stay pain free, and is completely reliant on us, and a variety of medical devices for everything in her life. It is because of her diagnosis that we got our other daughters tested. Thankfully, our youngest daughter, Kara, was only a few months old at the time we received the fateful call telling us that she too had this horrible disease.

Because of that early diagnosis, she was able to receive the gene therapy that quite literally saved her life. She now lives symptom free. She is advanced in communication, she rides her bike, she plays with Barbies, she goes to gymnastics, and she's at school as we speak. This is her.

These are all the thing that Libby over

here was robbed of because newborn screening doesn't exist for MLD, and to think if it did parents like myself would no longer go to sleep each night, knowing they may wake up with one less child. Siblings would no longer wonder how to play with her brother or sister, who could no longer walk or talk, and children like our daughter Libby, would have every opportunity in the world, all because of this heel prick.

We know and really good newborn screening tests exists. In the next six months the gene therapy treatment our daughter Kara received, will be FDA approved. When that happens, adding MLD to the RUSP will not only save lives, but save families from an unnecessarily tragic loss that affects each of them for the rest of their lives.

So I urge you to add MLD to the RUSP and help families like ours avoid losing one child in order to save another, and I thank you for your time and consideration today.

DR. CALONGE: Thanks so much, Kendra. I'm going to move on to Asmahan Safi, sorry Asmahan.

MS. SAFI: Hello. I am Asmahan, parent of Nora, and I would like to share her Metachromatic Leukodystrophy diagnosis journey. Nora at 12 months was a happy, normally developing child. She loved

eating food, especially spaghetti, and crawling up and down the stairs.

At 18 months she still wasn't walking, so we were referred to neurology. By her second birthday, Nora enjoyed her preschool, but she seemed often tired and dizzy. She loved watching Elmo and solving puzzles with her sister. We were going to the hospital several days a week for therapy, meeting with different specialists, and doing endless diagnostic testing.

We did rounds of x-ray, MRI, blood and urine tests. The hospital lab would often call the doctors back to reduce the number of tests in the panels because they couldn't take so much blood from her tiny body all at once. Shortly after that, Nora could no longer stand or feed herself. She was losing a lot of weight.

So on June 1st, 2018, she underwent emergency MRI revealing she had MLD. The doctor gave us this prescription. Go home and love her, it's terminal. A few weeks later we called the Milan Hospital hoping to enroll in a clinical trial that showed promising results, but they told us that it was too late. Her symptoms were too advanced. So that summer we told her sister, we told our families, and we felt like torture.

We arranged a visit from her grandparents to spend time with Nora before she lost her voice and her eyesight. We shared a last meal with her, rice and yogurt. We watched her body shut down. Nora, within three months of diagnosis would no longer sit or talk, or eat by mouth.

Here we are six years later. Nora needs around the clock care. We love her dearly every day. My spouse and I work now part-time. We now go to physical therapy ourselves. Her siblings spend time with Nora holding her hands in silence. With newborn screening there wouldn't be this painful diagnosis obviously. Families like ours wouldn't have to find it's too late and be deprived of access to potential life-saving treatment that is currently under review in the FDA, and approved in Europe.

I ask this Advisory Committee to take action. You have the opportunity to make Nora's life, and our experience no longer be normal. When the nomination is submitted, please consider the evidence and elevate it to a screening condition in the United States, thank you.

DR. CALONGE: Thank you, Asmahan. I'd like to check back with Maria Kefalas, and see if you have your internet problem fixed, and can join us? Hi.

MS. KEFALAS: Hello. My name is Maria

Kefalas, and I am the founder of Cure MLD, a global network of advocates for Metachromatic Leukodystrophy families. As you have heard from my friends, MLD is a devastating neurologic disorder that robs babies of the ability to walk, talk and feed themselves within 90 days of symptom onset.

Once the disease shows itself, it is a wildfire burning out of control. That is the way a neurologist described it to me. Destroying the white matter in the brain and the central nervous system. When my daughter, Calliope, was diagnosed with MLD, she uttered her last word within a month of her diagnosis. She turned to my husband and said, "Daddy."

She walked for the last time in the atrium of the Children's Hospital of Philadelphia, and her final meal was a yogurt smoothie. I do not remember her first steps, first word, or first meal with the clarity of the final ones. We, in the MLD community, are fortunate though.

We will soon join the ranks of the 5 percent of rare diseases with an FDA approved treatment. Experts in the field called OTL-200, a viral based gene therapy miraculous. The oldest U.S. patient is currently 13 years old, attends school, and has absolutely no symptoms of MLD. Without

newborn screening the only way to help our children, as you have heard, is to identify pre-symptomatic infants after the diagnosis of an older sibling. That means that the families who can access gene therapy now sacrifice one child, sorry, to save another.

This is a horrifying situation for our families, and the doctors who care for our babies. It is difficult to image a condition better suited for inclusion in the RUSP, given the curative power of the gene therapy and the devastating nature of Metachromatic Leukodystrophy.

I ask that the Board act as quickly as possible to include MLD on the RUSP. Thank you.

DR. CALONGE: Thank you. At this time I'd like to move on to Dean Suhr.

MR. SUHR: Greetings. You caught me on the side of the road. I was hoping to meet with all of you in person. My name is Dean Suhr, and first of all, I am an MLD dad. I don't talk about my girls too much with you all, but father of two girls with MLD. They were diagnosed in 1995.

Lindy at age 14 after a 6-year diagnostic odyssey and Darcy, age 10, only because we found MLD in her older sister. Darcy passed away in 1995 after a bone marrow transplant. My wife and I cofounded the

MLD Foundation in 2005. Tomorrow, 60 researchers advocates are gathering in Vienna for the fourth MLD newborn screening summit.

German MLD newborn screening started in 2021, it's using the Gelb assay. To date, three sites over there are active. We also have a site in [indistinct] New York. Today some 160,000 samples have been screened using high-throughput tandem mass sulfatide screening, followed by enzyme and genomics as the second and third tier.

Four babies have been identified to have gene therapy. One is waiting their turn for gene therapy. They waited for months for their therapy. The incidence is about 1 in 40,000 in their published four months of trial. As has been mentioned, gene therapy was approved by the EMA in December, 2021, so Europe has access to this therapy, and they have screening at least in Germany, and working with other countries.

Last August, Orchard Therapeutics launched the IP, submitted their PLA to the FDA with RPV and RVAC designations. Since then, prior review has been granted. Our producer day is March 18th, so we all circled that on our calendars. Excuse me, as you have heard pre-symptomatic diagnosis to access this therapy when it's most effective is not possible

without [indistinct].

I spoke in the last meeting about Professor Gelb's work to develop the published genotype, phenotype scaling back the knowledge and matrix for the 76 percent predicted value. I hope you've had a chance to look at that. I will send that up to you all.

We're adhering to the Committee's rules regarding having an approved therapy before we submit our RUSP nomination, but as you heard, we're all looking to March 18th. So expect to be seeing that come before you probably the second meeting from now.

Those of you watching for state labs, we have met in your labs or APHL needs over the past seven or eight years, know that MLD Foundation wants to work with the labs and the public health systems to first identify the challenge and opportunities to implement newborn screening, so now that our nomination date is much more finite we'll be certain that would be more urgent to help you get started for implementation.

Today you're meeting, the first meeting of some of the MLD families, and getting the feel for the vital importance of the early diagnosis of MLD. We hope when the Committee meets, and hopefully in person in May, which will be the time that you would

vote to add this to, or send this to expert review, that we can bring families and some of these affected individuals, so that you can personally experience the curative nature of the early diagnosis and gene therapy.

And a quick mention about the RUSP roundtable. We are currently planning that as well.

DR. CALONGE: Please wrap up Dean, please.

MR. SUHR: For when you first next meet in person, and we hope that that will blend in well with EveryLife is doing, what you're doing this afternoon. Thank you all for your continued work in newborn screening, and keep at it. We really appreciate that you're addressing challenges, and struggling with them, but working on them and making progress. Thanks all.

DR. CALONGE: Thanks Dean. Next, I have Kim Higbee.

MS. HIGBEE: Hi, yes, good morning. My name is Kim Higbee, and I live in Jacksonville, Florida with my husband and two young daughters. I'm here today as a mother and also as a Board member for the Hope for PDCD Foundation. As my rare disease community prepares to submit a RUSP nomination in 2024 for Pyruvate Dehydrogenase Complex Deficiency, I wanted to take this opportunity to begin to raise

awareness in the newborn screening community because even though PDCD is one of the most common, neurodegenerative disorders associated with abnormal mitochondrial metabolism, it is still very much unknown.

My youngest daughter, Harlow, was diagnosed with PDCD at nine months old, but our diagnostic journey began at birth. After a healthy pregnancy, Harlow scored low on her APGAR test, and we were told she had congenital hypotonia and upwards of 600 things could be the cause of that.

Fortunately, our story is different from many, and we had a pediatrician who fought alongside us to get us what we needed, and to whom we needed to see as quickly as possible to get answers. But that still meant, what I like to call those stepping stone procedure of what insurance will approve for testing. For us that included a micro array, a DNA methylation test, a brain MRI, a leukodystrophy panel, and finally the whole exon sequence.

Sadly, those were nine miserable months that Harlow was only awake for around 45 minutes at a time, and was likely suffering from lactic acidosis causing metabolic distress that my husband and I mistook for colic cries. Shortly after diagnosis, we got Harlow on the ketogenic diet, since PDCD patients

can't process carbohydrates for energy, we saw an immediate change on day one.

It was like an awakening for her, and her personality began to shine through. Harlow was now almost two and a half years old and showing progress every day, although I still question what it would be like had we started Keto in the first week of life. While we can't undo that damage for Harlow, we can help others that come after us, and save the future parents from the long diagnostic journey.

And before I wrap up I'll just share. This is Harlow today, this little one here. I don't know if you can see. As happy as can be staring at her big sister, so. Thank you very much for the time.

DR. CALONGE: Thank you very much as well. And then we have Frances Pimentel.

MS. PIMENTEL: Thank you for the opportunity to speak today. My name is Frances Pimentel. I live in Folsom, California. I'm a rare disease mom, and a produce designer for Bobbie infant formula. On behalf of Hope for PDCD and the PDCD community, thank you for the opportunity to speak about the upcoming RUSP nomination for PDCD.

My daughter, Violet, has a treatable mitochondrial disease known as Pyruvate Dehydrogenase Complex Deficiency, or PDCD. As a second-time mom my

maternal instincts told me something was very wrong when Violet was sleeping too long in between feedings, not tracking objects, difficult to feed, and overall just not thriving.

Countless pediatricians, ER doctors, and even neurologists could not have been more incorrect when they told me there was no urgency in finding answers, and that some day she would catch up with her peers, and that everything would be fine. My instincts told me to disregard their advice, and instead I advocated to get my daughter admitted to UCSF for a full diagnostic workup.

Every day I thank God that I did that. As it turns out my daughter has a mutation on the PDHA1 gene, causing a treatable mitochondrial metabolic disease. As the disorder of carbohydrate metabolism, children with PDCD need a ketogenic diet, and the earlier you start this therapeutic treatment the better the outcome.

With PDCD, carbohydrates cannot be used for energy, and every day that patients are not in ketosis means that lactic acid is building up in their system, especially in their brain and their central nervous system. My husband I have no doubt that my daughter's medical ketogenic formula is not only keeping her alive, but allowing her to thrive.

Within days of being in ketosis, her baseline lactic acid went from a 5 to a 2. She started babbling, talking to objects without any visual delay, and making progress toward milestones that were previously missed. Today she is no longer content to lie still, and we are even having to baby-proof our home as she has begun crawling.

She is still 100 percent dependent on a feeding tube, after losing her suck, swallow reflex at four months, but we are still so grateful for her, and for getting the diagnosis so early. Unfortunately, the 9 months of brain damage can never be undone, but we hope to help the families that come after us. We know from a pilot study done in Ohio that PDCD occurs in 1 in 40,000 live births, making it slightly more common than ALS.

In that study, and in others in Colorado and Pennsylvania, it was shown that using the biomarkers, proline, alanine, leucine and lysine, which are already included in existing screening methods, children with PDCD can achieve early detection through newborn screening.

And I'll just share a photo. This is my daughter, Violet. She's beautiful. Thank you for your time today.

DR. CALONGE: Thank you so much, Frances.

I want to pause and thank everyone who did public comment with us today. I want to thank EveryLife for the studies and written comments they provided for consideration and review, but I especially want to thank the parents who shared the personal journeys of themselves, their families, and their children affected by heritable disorders.

It's an important part of the Committee. It's one of the reasons the Federal Advisory Committee Act was created, was to include the voice of those affected in policy decision making. And I really appreciate the courage, the effort, and the time it takes to present in front of the Committee.

With that, although it's not on the schedule, I'd like to pause and take a five minute break since we have been sitting for a while, and we'll get started back again in exactly five minutes, so thank you.

ACHDNC Decision Matrix Tool

DR. CALONGE: We're going to start up again, and I'm just going to remind you back in May, Dr. Kemper provided the Committee background information on how the decision matrix tool was created, and I followed up with some suggestions for updates to the matrix tool. The intent of the

proposed updates I'm sharing again today, is to make the decision matrix tool match our current practice.

And it's not moving the goalpost, which I want to make sure we're clear about, or to change the criteria for nominated conditions, but it's really to assure that the decision matrix reflects how we've actually functioned over the past decade. Specifically, in the original matrix, B ratings were not intended to be recommended to be added to the RUSP, and yet the Committee has a practice of discussing these, and has recommended these, and they have been added.

So, looking at that, and thinking about the discussion we put together a small group of previous and current Advisory Committee members, including two former Chairs of this Committee, Drs. Joe Bocchini and Cindy Powell. And we discussed the proposed updates to the matrix, and I'd like to give you a presentation of where we landed. Can I have the next slide please?

I think it's important to recognize that the tool is meant to support decision making, it's not meant to make the decision, so it's a guide that we can use to help support our thinking as we move forward in one of our activities, which is to recommend addition of conditions for consideration

for addition to the RUSP. Next slide.

The summary of the suggested changes are actually fairly small, but we want to separate out elements of public health readiness. Let me just do this real quick, and feasibility from the evidence review and decision regarding the magnitude of net benefit and certainty of net benefit.

And then we want to move away from the grade classification to something that's less -- has less social construct, and say instead a designation. Next slide please.

Noted -- talking about program assessment of feasibility and readiness, we recognize that the current assessment approach has not impacted recommendation decisions. There needs to be an improved approach to assessing barriers to implementation, and public health impact. And that assessment should be evaluated separately from the evidence-based decision to add or not add a condition.

The inclusion of an assessment of public health impact, including cost, is a required element of the matrix by statute, and is also critically important in considering addition to the RUSP. Next slide.

So getting to the matrix itself, the

changes include a single A designation of high certainty of substantial net benefit. And then a new B designation that includes either a moderate certainty of substantial net benefit, or a high certainty of a moderate net benefit. Then create a C designation that includes moderate to high certainty of a zero or small net benefit, or net harm.

And then an I designation corresponding to low certainty, which indicates that the evidence is currently insufficient to assign any other designation. Next slide please. So every designation will have a decision attached to it. Conditions within a designation will be forwarded to the Secretary with the recommendation to add to the RUSP.

Conditions with a B designation may be forwarded to the Secretary with a recommendation to add to the RUSP after discussion, and a separate vote. Conditions with the C designation will not be forwarded, and conditions with an I designation will not be forwarded to the Secretary, but evidence gaps will be identified and shared with nominators. Next slide please.

Thinking about the B designation and action, here's the proposed process. Based on an assessment of the magnitude of net benefit, and a

certainty of net benefit, the Committee would first vote to assign a B designation. Then, based on additional discussion of the evidence an assessment of the anticipated impact of adding the condition in terms of individual, family and public health benefit, the Committee will vote on whether to recommend adding the condition to the RUSP.

This separates agreement on the evidence from agreement that the condition should be added to the RUSP, which we felt were two kind of separate thought processes and judgments that should be separated, but linked for these B designations. Next slide.

So here is a summary of the suggested revised matrix, the A, B, C, and I with the descriptions that I've just presented, and then the actions that we also talked just a little bit shorter. Next slide please.

So the matrix requires judgment, and this is an important part of all evidence-based practices. You can't look through evidence, the decision process, that doesn't include the word judgment in some place. So the two areas of judgment are net benefit and magnitude of net benefit.

In terms of certainty of net benefit, there are well established approaches for the decision. We

would suggest, or adopt, or revise the criteria used by the U.S. Preventative Services Task Force. Certainty is based on the evidence. It's based on the quality, coherence, consistency, amount and specificity of the evidence.

And so it's an epidemiologic consideration that again, is -- it does require judgment, looking at the elements, but otherwise I think is well-established in the evidence-based world. Now, the magnitude of net benefit is more complex, and especially in the setting of creating new levels of net benefit that we talk about as substantial and moderate.

The Committee will need to outline at least rough criteria that we can use to make this judgment consistently over topics and time, and that work has not been done. The listening sessions today are intended to start providing us with the information we need to map out this decision making around net benefit.

So we hope that as we break up into different groups, we participate in answering the questions and providing input from different perspectives about both benefits and harms. Next slide please.

All right. Coming back to public health

impact assessment. So, by law, our recommendations for addition to the RUSP must include an assessment of public health feasibility and assessment. Since we are asking public health, state public health, laboratories and state public health newborn screening programs to implement these screening recommendations, we really need this assessment in order to help put the entire package together, and reach implementation, which I think is what we all hope to achieve.

Our ad hoc topic group did not read a conclusion of how to best do this, and we would like to consider creating a separate group to work through those issues. I wanted to provide examples of questions that could be asked. Is testing for the condition feasible through all state health departments in the next three years?

And there's a lot packed into that, so the state health department is kind of the hosting agent that recognizes the state public health laboratory, but also the follow-up and medical care system necessary to complete the implementation from screening to diagnosis to therapy and follow-up.

The three years came from kind of what we learned in doing the assessment the way we were doing it before, was that every state lab would end up

saying yeah, if we had the right resources and everything fell into place, we could do this within three years. So this becomes a question that can we assess that? Is it feasible in the next three years?

And then the second question will be will all state health departments be ready to implement testing within the next three years, similar to the first one, so we have the assessment of feasibility and readiness. And then the last question, which is also included in our statute, what is our best current estimate of the total cost of testing, follow-up testing, and arrangement for treatment for newborn screened?

Here we know that cost estimates are hard in talking to the evidence review group, I know they struggle and work hard on this with every condition. And what we'd like to do is see at least a point estimate and range, and this information is actually very important in fitting into the answers to the previous two questions. Next slide please.

So that would complete the matrix, but now you see a separation out in the public health impact assessment from the evidence assessment, and while the questions in the bottom part of the matrix are there for suggestions, and that we need to kind of work on those moving forward, the feeling, or at

least the proposal is that the matrix would look something like this moving forward. Next slide please.

In talking about feasibility and readiness, we need to really talk about what we want to achieve with that process. In terms of identifying the real barriers, and the solution to those barriers that would lead to implementation within three years. We'd also like to identify support that not just the Advisory Committee, but also CDC and NIH, and of our partner agencies at the table who participate in discussing the conditions and making recommendations for additions.

How can we come together as different federal agencies to support implementation moving forward? We'd like to assess the level of support and prioritization from decision makers in the individual states, recognizing that this varies state by state, and could include newborn screening advisory committees, state public health laboratory directors, state public health department executive directors, governor's offices, and key legislators.

I think really assessing how we engage all of the major decision makers and policy makers in assessing readiness, and getting us ready to implement new conditions will help move quicker into

implementation, and would help address the fragmentation of implementation that currently exists in the screening system for the conditions currently on the RUSP.

This would give us a set of actions that the assessment results would then prompt. Next slide please. So, I'd like to talk with the Committee about changes to the matrix, and about creating an ad hoc group to further assess a process to assess public health impact, recognizing that we want and need to do this in partnership with the broad concepts of state newborn screening programs, and think about a robust method of collecting feasibility readiness and public health impacted elements.

I think that's the last slide. One more maybe? Yeah, the other one is just to recommend the top part of the matrix to remind you, and with that I'd like to open it to discussion, starting with Committee members. I think we could probably do that.

As people are thinking about their questions, I want to thank the time and effort that ad hoc topic work group put in. There was a lot of years of experience at the table, and it was good seeing old friends, and wrestling with similar issues. Thanks, Michele, for putting your hand up,

and please go ahead.

Committee Discussion

DR. CAGGANA: Thank you for that. I think the matrix, as you put it up on the screen for us, and was in the book is much clearer, and it gives us a good way to make those assessments. Regarding the public health impact, I think that that first bullet you had about the feasibility, implementation within three years.

I think instead of saying maybe state health departments, maybe you should say the newborn screening system, because that will help you ensure that you're encompassing not only the laboratory, but also follow-up and clinical care. I think a lot of times when people talk about newborn screening, they're only talking about the lab. And I know I echo, I'm channeling Sue Berry here, but I think we need to make sure we understand that we're encompassing the entire system, and maybe by being a little bit more clear on that first point, thank you.

DR. CALONGE: I appreciate that, and of course entirely agree with you. And this is the Committee, even after the last discussion, or the first discussion of the morning that always reminds me of the Chinese proverb that words are important,

so I appreciate that. Ash?

DR. LAL: Yeah. Just a quick comment on if a condition is classified as C based on the evidence, the extent of the benefit, then would that still go through the feasibility, the analysis, or that would not? Are these happening in the panel, or is it the post-determination of the designation A, B, C?

DR. CALONGE: You know, Ash, it's an outstanding question, and one that the ad hoc topic group that looked at the matrix discussed, and didn't come to a conclusion. Currently, the approach was that they would be done concurrently so that the decision to add to the RUSP would not be if you will slow down by the assessment process.

The issues that came up are that not knowing exactly how the testing will occur, not having all of the information makes it more difficult for laboratories to engage in that assessment concurrently, and that's something that I think we would like the ad hoc group on Newborn Screening System Feasibility and Readiness to kind of take on because we couldn't quite answer it.

But you're right, if you got to C, the idea is that you wouldn't need to have assessment because you weren't going to add it to the RUSP. Shawn?

DR. MCCANDLESS: Thanks. This kind of

follows on to Ash's question, and that is can you talk a little bit about I think the recommendation for an A finding is that it will be passed on to the Secretary -- it will be recommended to the Secretary to add to the RUSP.

How would you see the feasibility of readiness evaluation fitting into that if the A automatically moves something. If an A designation automatically moves something on to the Secretary with a recommendation to add to the RUSP?

DR. CALONGE: Yeah. And Shawn, that's an important clarification, so I appreciate that. From an evidence standpoint it would move directly onto the RUSP. But you still have to complete the public health readiness feasibility and impact assessment before that can be complete, and so it would have to await that. So yeah, it doesn't have any barriers. I guess maybe the way to say it is it doesn't need that second vote, but it still needs that assessment.

It's possible, and this came up in the discussion with the ad hoc working group, that the evidence would support an A recommendation, but that it might never be feasible or ready to do in C, public health newborn screening systems. And so thinking about alternative approaches might be necessary. But you're right, that was a nuance that

we were, I will admit, I think we were so focused on the B's, it's a good question. I appreciate it. Carla?

DR. CUTHBERT: Thank you for that presentation. This is just a bit of a minor tweak with respect to the questions, the proposed questions for assessment, especially related to cause. Perhaps instead of saying the current estimate of the total costs, maybe you could include a range of estimates as opposed to the best current, since it really depends on the general approach.

I know that's the nuance, but it might be a little helpful instead of looking at absolutes.

DR. CALONGE: I really appreciate that comment, Carla, because that's what I was trying to get at with the range, and maybe I was too hopeful about there being a point estimate. But the idea is we will recognize that there's a range, and it's less a range in terms of a statistical range, like an average with dispersion assessment, but more of what do we think, you know, given what we know, or we can assess, or the assumptions we can make would be the lowest end of the range as well as what might be at highest end of the range.

So I think that's the clarification we can make, and I appreciate the comment. Debra

Freedenberg?

DR. FREEDENBERG: Hi. Good morning. I apologize for the noise. I've got roofers on the roof, so I think that the feasibility assessment, the criteria have been laid out and assessed pretty well for the laboratory component, but I still don't think that we have an adequate assessment of the follow-up in the clinical portion of this in terms of what would we be assessing, and what questions really need to be answered within those two components of the newborn screening system.

DR. CALONGE: I couldn't agree with you more, Debra, and I appreciate your comment. And I tried to put all the words in there. It is -- it's almost second nature to fall back and pick on the labs, so I apologize for that. So we always have to remember that this is a system. The laboratory is an important component, but not the only component.

And as we talk about feasibility and readiness, it has to think entirely across the entire system, so that's why we couldn't get to it in an hour and a half with the first ad hoc group. Susan Berry?

DR. BERRY: Thank you. Sue Berry from the SIMD. I want to pile on on this whole aspect with regard to the further parts of the system that have

really never been considered in making any of these evaluations. I'm going to suggest hopefully that as you create the ad hoc group that you make sure that representatives on whom this would have an impact are able to lend their voice to this conversation.

The other comment that I would make is that one of the other things we've never considered, and I don't know if it's feasible, or even should be, is that the relative access to care for affected babies is an important element. When we start approving things that cost a million dollars, or two million dollars, or three million dollars or more per dose per treatment, that means that there's a likelihood that those will not be applied evenly across all babies, and we run a risk of being incomplete in providing access to care.

And I don't know how to ask that question on a longer-term basis, but I know it's a high impact issue as we have more lifesaving, very expensive therapies made available for treatment of potentially newborn screened disorders, so don't know how to get that, but somehow we must.

DR. CALONGE: I think it's a great comment, Sue, and you know, in coming back to the Committee after a few years off, I remember when we were doing costs I specifically asked Alex whether

costs of treatment were included in the calculations of cost, and he reminded me that they are not and have not been included.

And whenever you do cost effectiveness analysis, you always have to assume all of the costs, including the costs of treatment, and so that would be a major change, I believe, and it's something I think it would be a good additional aspect of the ad hoc committee looking at this specific element to consider.

DR. BERRY: I'm coming at it not just from the aspect of how much it costs, but how fair it is.

DR. CALONGE: Right.

DR. BERRY: And access to care, and that's --

DR. CALONGE: Yeah. How that translates to equity, and thank you. I didn't mean to gloss over that important aspect. Scott Shone?

DR. SHONE: Thanks Ned. Scott Shone, Org Rep ASTHO. So just two real points. One, every time I look at the proposed designation, revised designations I find something else I want to comment on, and I wanted to just highlight that you know the proposed C says conditions with C designation will not be forwarded to the Secretary.

And I says will not be forwarded to the

Secretary, but evidence gaps will be identified and share with nominators. I think it's important that no matter nothing was -- I think the communication piece regardless needs to be highlighted and part of it.

So to C and I, I don't know why wouldn't we share opportunities for improvement of a C? And I think that's not -- well I, having participated in the ad hoc group, I don't think that that was intentional, but now that I see it, I do think that it's probably important for us to call out, but as you do currently in your role, and your predecessors in that role, there is constant dialogue with nominators on what was submitted, and what are opportunities for improvement moving forward.

So that was the first thing I wanted to call out is an opportunity to tweak this a little bit. The second, I wanted to highlight something that I got to participate in, in a different role before I was lab director in North Carolina, where I got to work with Florida's Newborn Screening Advisory Committee. Florida passed a law several years ago that after a condition was added to the RUSP their advisory committee had a timeline to review that condition, and recommend or not, adding it to the state's mandated panel.

And they developed a process in contracting with a group to look at, basically do a review of their system with respect to readiness for addition of the condition, and that included interviews with a variety of clinical practices and specialists that identified as part of the Advisory Committee's evidence review, Alex's work, but also through department interviews based within the state.

And then when that report was generated and showed a variety of things from cost, estimates of cost to private insurance, but also part of Medicaid system, but also whether or not the medical system and specialty care had sort of adequate bandwidth, or specialists, and there were some conditions that were reviewed, where it was identified that there were certain things that needed to be put in place before they might want to go ahead with moving forward.

And so, you know, I point to that as a potential resource for any future ad hoc group to look at where they include those documents, and knowing that Florida, you know, is a sunshine state, those documents are probably available online to anybody who would want to see them as part of the Advisory Committee, so.

DR. CALONGE: Thanks Scott for both of your comments, and well said and taken. And I took notes.

I appreciate it. Bob, you have the last statement before lunch today, so.

DR. OSTRANDER: Yeh. Two things. One is although I agree with -- it's Bob Ostrander, AAFP, org rep. While I agree with Scott that certainly for both the C's and the I's we should get back to the nominators. The way I read that is the I kind of was the ones that might have a little star next to them where they would be potentially more likely to be considered for the earlier expedited re-review like we talked about last meeting with Krabbe.

So I do like those different categories, even though they both need feedback to the nominators, I think the I, because these are condition where we had enough uncertainty, that with a little more evidence we might want to do an expedited re-review and not have to go to a new application process.

But I like those segments, and you can flush them out however you like. My other comment quickly, to tag on to what Sue Berry said, I think that the DEIJ aspect of expensive conditions could cut both ways. Certainly if we recommend a real expensive condition to RUSP, we may be recommending a condition that could worsen its application.

On the other hand, there has been movement

that anything that's been recommended to the RUSP must be covered for everyone. And it's possible that recommending expensive things to the RUSP may actually reduce inequities.

Not -- I don't have an answer one way or the other, but I think we should bear in mind that you know, sometimes by adding something to the RUSP we may be actually reducing disparities where right now because it's not on the RUSP, only the certain, fortunate people that can run and get an early diagnosis without earlier screening, and then paying for it get treated, where the ones who can't do that when they've got a kid who's, you know, having some early symptoms maybe -- isn't going to get diagnosed.

So, my ideal is that adding things to the RUSP promotes equity, and doesn't worsen it, but it obviously could cut the other way.

DR. CALONGE: Yeah. I appreciate that. I think mandated coverage we always recognize that somebody pays for mandated coverage issues. And it comes out in our insurance premiums. It comes out in our tax dollars. If Medicaid at a state level is restricted in getting larger, if you're going to tax limitation state like Colorado, then if you spend more in one area you have to back off in another.

So there are adverse consequences in

multiple other areas that we always have to think about when we talk about costs, but I appreciate that. This is a way to think about more equitable access over time. All right. This is great. I think I heard a lot of positive comments. I think what I would like to do is move forward with staff here in reaching out to folks about creating this ad hoc committee on Public Health and Newborn Screening System, Feasibility, Readiness, and Public Health Impact.

And we'll start working on that at the end when this meeting is over and try to get a group starting meeting as early as before the next meeting. And with that, Shawn -- oh I'm sorry Shawn.

DR. MCCANDLESS: That's okay. Very quickly, would it be possible for someone at HRSA to try to track down the report that Scott described that they made for the State of Florida, and make it available to us?

DR. BROSCO: I've already emailed them.

DR. MCCANDLESS: Thank you.

DR. CALONGE: Unless there are further comments or questions, I suggest we take a break for a half hour for lunch, and then we'll reconvene promptly at one o'clock Eastern, and for Shawn that will be nine o'clock Colorado time. And eight

o'clock if you're in California, so see you all soon.

ACHDNC Conflict of Interest

DR. CALONGE: I want to welcome everyone back to the afternoon session. For those of us who it is afternoon, and thank you all again for attending today. Excellent discussions this morning. I think just to really moving of a comment session as they all are, and again I appreciate the commitment of all of those invested and interested in newborn screening for spending time and effort and emotion with us today.

Moving onto the afternoon, back in May you remember I presented a proposal to address conflict of interest, both for Committee members and organizational representatives. We took the information that we discussed at that meeting, and Jennifer Kwon and I reviewed FACA policies, and reviewed policies and procedures from other federal advisory committees.

Dr. Kwon will now present on proposed recommendations for how the Advisory Committee should vote on conflict of interest assessment moving forward. Just to remind people, Dr. Kwon joining the Committee in January of 2022. She is a Professor of Neurology at the University of Wisconsin School of

Medicine and Public Health, and the Director of the Pediatric Neuromuscular Program at the American Family Children's Hospital.

Dr. Kwon is trained in pediatric neurology and neuromuscular disorders, and it's just an outstanding small group partner, so Jennifer, if you will take over that will be great. I think we'll put the slides up.

DR. KWON: Great. I hope people can hear me okay.

DR. CALONGE: Yes.

DR. KWON: Great. So earlier Natasha apologized for having very text dense slides. I don't think you've seen anything yet until you get into this presentation. But it is, next slide please. Oh I'm so sorry, I must have re-muted myself. I apologize. So this is a very text heavy presentation, so in terms of reviewing the conflicts of interest I think that there was a desire to make sure that all of the Committee members potential conflicts were transparent to the public.

Our processes are designed to assure that decisions are based on evidence, and because we all have varying degrees of interest and passion about newborn screening, or the disorders being discussed, those interests need to be made public. As the

conflict of interest processes have become more complex over the past decade, we want to assure that decision makers in these studies base their votes on evidence, free from other influences.

And after review of methods in different groups, as Ned said, we've decided to model our processes, or our proposed processes after the CDC's Community Preventative Services Task Force. Next slide please.

So the proposal is this. Prior to a meeting all voting members will review the topics to be voted on, and complete a disclosure form that covers financial conflicts of interest, potential business and professional COI and potential intellectual conflicts. HRSA staff and the Advisory Committee Chair will review these statements and decide whether the member should have restricted participation.

If a restriction is being considered, the Chair and staff will schedule a call with the member to discuss the potential conflict. And please note that disclosure and actions on any decision on restrictions are separate on the disclosure, it may not lead to a restriction.

And the potential restriction decisions are that there be no restriction, and no public

disclosure. No restrictions, but with public disclosure of the issue done by the Chair in opening comments. Participation and discussion, but restriction from voting announced by the Chair in opening comments, and recusal and restriction from all parts of the topic presentation and discussion including the Committee member leaving the room, or the remote meeting, and this will also be announced in the open comments. Next slide please.

So the first conflict are financial interests, and this was the primary emphasis of the COI forms that we filled out when we joined the Committee. These financial conflicts of interest referred to in –

DR. CALONGE: Jennifer?

DR. KWON: Yes?

DR. CALONGE: I'm sorry. We're one slide behind, so we're looking at the possible restrictions slide.

DR. KWON: Okay. Sorry.

DR. CALONGE: And now we're on the financial interest slide.

DR. KWON: I'm sorry. I think I have something I was reading from, and I wasn't looking at the slide itself. I apologize.

DR. CALONGE: Okay. I think we're good.

DR. KWON: Okay. So, what constitutes a financial interest refers to investments or interests in entities that could influence, or give the appearance of influencing the outcome of the decision, so entities could be individuals, organizations and corporations, or other groups of established or future business in the matter of decision.

A relevant financial interest, and that will be listed on the next slide, is a situation in which a Committee member has the potential for direct or indirect financial gain or loss related to the recommendation vote. And we should also -- members should also disclose financial relationships for themselves, their spouse or significant other and dependent children. The cutoff is $1,000.00 or greater for the previous year. Next slide.

So financial interests include ownership of individual stocks, or other significant proprietary interests or investments in any third party that could be affected by a decision. Having an employment, independent contractor or consultant relationship, or other contractual arrangements, whether written or unwritten, with an entity that could be financially or reputationally affected by a decision. Receiving patents, royalties or licensing

fees from a proprietary or private business entity, excuse me. Receiving a research grant awarded to you as an individual, or a primary investigator, co-investigator, consultant or subcontractor from a proprietary or private business entity, or corporation foundation, and this does not include federal or nonprofit research grants. Next slide please.

Financial interests also include receiving compensation for participation on the governing board or advisory council of a proprietary private business entity, or any other entity, including nonprofits.

Participating in a speaker's bureau, receiving honoraria, travel or gifts from a proprietary private business entity, and receiving payment as an expert witness in a trial or legal setting, for either the plaintiff or the defendant associated with such a proprietary private business entity, and receiving compensation for services by parties having a financial interest.

And those are, I think, fairly clear in terms of the financial interest. Next slide.

I think a little murkier are potential business and professional interests, which many of us have with entities or stakeholders related to newborn screening. So business or professional conflicts of

interest refer to relationships or activities not otherwise disclosed as financial, that could influence, or give the appearance of influencing the Advisory Committee decision.

Again, examples are listed on the next slide, but it's essentially a situation in which a Committee member has the potential for business or professional gain or loss related to the Committee decision. And again, members should disclose their own business or professional relationships, as well as those of their spouse and dependent children. Next slide please?

So examples are giving public comments and testimony, which include serving as an expert witness made on behalf of a business or professional organization. Having a leadership role in a professional organization, or I assume, advocacy groups, society, journal or certification body. Advocacy or policy positions on behalf of an entity.

For this section, we will want you to disclose relationships with governmental organizations, non-governmental organizations, including nonprofits, private organizations, professional societies, and other organizations that you have reason to believe may benefit or be harmed by findings. And include serving in the following

roles: board member, director, expert advisor, other leadership positions, or having received grant funding. Next slide please.

The third category is potential intellectual interests, and it's recognized again that here they're likely to be numerous potential conflicts, again because of Committee members interests in where disorders, often particular rare disorders, as well as newborn screening activities. Members are chosen for their national reputations on relevant issues, and their work may be sufficiently well-known, so that audiences might question the objectivity of the process if members are known to have taken leadership roles and discussion, or even a vote on topics.

So a member -- as an example, a member may hold strong personal views on the effectiveness of particular interventions, and may be unwilling to accept evidence to the contrary. The same holds true for people expressing a strong moral conviction that may influence the members scientific opinions.

Other examples are membership in a lobbying or advocacy organization, serving as an expert witness, public comments, or other indication of strongly held beliefs, and intellectual property rights, including books, journals, et cetera. Next

slide.

For our organizational representatives, we recognize that they should not be held to the same standard as voting members. They are appointed to represent interests that include advocacy interests of their own society, for example. However, while organizational representatives should not have COI related restrictions, they have special status and access to participation in Committee discussion, so the proposal is that organizational representatives should annually disclose whether they receive funding from private or proprietary businesses, and include in that disclose how much and what percentage of their operating budget, if relevant, such funding represents. And this information should be made available to Committee members.

So, this is the end of the topic. I've flown through it fairly quickly because the topic is pretty well represented in the briefing book, and then the form that we're asked to fill out also has a lot of explanations and examples, and so, should be relatively straight forward, so I would say we're open for comments and questions. Ned did you? Oh my goodness.

DR. CALONGE: I did. I raised my hand because you are still in control.

DR. KWON: Very good. Can I stop being in control?

Committee Discussion

DR. CALONGE: Yes. As we went through especially the last two things for professional and business interests, I just wanted to step back in and say remember that once you disclose -- and actions are separate. And so, you might have something that you identified as a potential, intellectual interest, and that you tell us about it, and working with staff we could say yeah, but we're not concerned about that, so there's no action taken.

If we had any questions we would call and have a question with you before dialogue, before making any decisions about a potential action. So I think that separation disclosure and action is really important.

The second thing I wanted to say, having gone through this for the Advisory Committee, for the Community Task Force. Once you fill out the form once, it's easy, so then you only have to see whether or not the topic in the upcoming meeting would make you change anything, or add anything. And so, while it might be a little tough the first time, just like the OGE 450, which we all know and love, it will come

back to you completed the way it was the last time you did it.

And you just have to say are there any changes. So, actually after the initial investment it's really quite easy. So those were just some things I wanted to add before we open it up. And the first person I see is Shawn McCandless.

DR. MCCANDLESS: Thank you. Thank you all for your hard work on this important issue. Shawn McCandless, I'm a Committee member. Two questions or points. The first is a point. I think that we talk about conflict of interest, but I think there's also a really important transparency issue that we need to address about duality of interest because I think all of it, you know, you allude to the point that all of us are on this Committee because we bring some expertise, and some experience and maybe even represent particular points of view that are going to impact some of the decision making.

And so it seems really important to me that we have a mechanism for allowing people to know what the duality of interest that an individual might have are. Whether or not they actually rise to the level of a conflict of interest, it could lead to them stepping out.

So I think there's value in distinguishing

duality of interest, which is present all the time, and a conflict of interest, which raises a higher level of concern and need to be addressed potentially, as you say, with some negotiation around what the impact of that would be on discussion.

So, I guess the question there is: is there a discussion of including some statement about duality of interest. And then the second question, and I'll mute myself, is there any reason to think about applying this to the Evidence Review Group and the expert panels that we employ as well?

DR. KWON: So can I address the duality question? And Ned, correct me if I have the spirit of this wrong. I think, Shawn, we recognize that we all bring that duality. I think part of this process is to make maybe the public aware that we're aware of this potential appearance of conflict.

And that this is -- so we're not necessarily calling ourselves out as saying this is a conflict, this is a conflict. We're sort of saying this is an activity that I participate in. It's maybe well-known that I participate in this activity. I am going to share this, and explain why I don't think it represents a conflict.

So, I think that that may address part of the duality question. And in terms of the Evidence

Review, I think I'm going to not answer that, and I'll let Ned chime in for those answers.

DR. CALONGE: Yeah, it's a good -- well it's a great question, and I do think that I would like to circle back around with staff, and then the lawyers at HRSA, because I agree, Shawn. I think if you're participating in helping the Evidence Review Group Make decisions around the presentation of the evidence, the strength of the evidence, the certainty of the evidence, I think understanding and reviewing conflicts to be transparent for that process will be important.

But we haven't actually talked about that, and we wouldn't need to do it for Committee members and any org reps that are included, but we would have to do it for other subject matter experts, so can I get back to you on that one? Okay. Ash?

DR. LAL: Just reviewing materials, the timeline. I think my comment is that is there a shift, a slight shift on how to -- who determines that there's a conflict? So I think getting used to the model currently where in societies that we're a part of, or that during a lecture, you have to ferment not things that are relevant to a topic being discussed, but get from everything, any research related, or other financial conflicts.

And then the organization reviews it and gets back to it. And I think this is what we've done in the past in this Committee too. But now in addition to that prior to each meeting we would also look at the topics of the RUSP, and then decide if anything has changed, or?

DR. CALONGE: Right.

DR. LAL: So is that a shift, or is that not a shift?

DR. CALONGE: I think there are two -- thank you for the question. There are two shifts. One being that we will review it as a topic specific assessment prior to every meeting, so that's one. And the second big shift is the addition of potential professional and business -- professional business, and intellectual conflicts, or to Shawn's issue, dualities. Kind of understanding and being transparent about people's other roles and expertise.

And whether or not, you know, being transparent about that, so that the public can trust we're making decisions based on the evidence and not bias. So those are the two biggest changes. The addition of professional and business conflicts is moving very rapidly through many other governmental panels. So you know, Jennifer and I worked mainly with the community guide partly because it's public

health.

But partly because I was involved in helping them put that together, and doing the assessment forms for about three years before I rotated off that panel. But we modeled ours closely after what the U.S. Preventative Services Task Force has done, which is a group that also when they make a recommendation of an A or a B nature, has big ramifications in terms of costs of medical care system, and economic benefit to clinicians and manufacturers.

And so that new lower level of $1,000.00 came directly from the U.S. PSTF. So I think what we're doing -- what I'm asking the Committee to consider, is to adopting the approach that other national panels whose decisions carry important public health and economic impacts, to follow the same, similar process. Jeff?

DR. BROSCO: Ned, I think I've heard you say in the past that part of the way that you've thought about this, and for example on NASEM panels we'll say you know, yes, you have this duality of interest. Does it prohibit you from being able to make a, you know, a non-biased decision. Can you say more about that?

DR. CALONGE: So, the current process,

which we've used in the past, is other than the financial interests as outlined in the OGE 450 and the system that HRSA has for addressing that and asking people about their investments. Those have happened in the background, but what I noticed at NASEM was this question about -- I'm sorry.

And then once we did that if the topic came up, we would just say if you think you have a conflict of interest, you should recuse yourself. So we asked each member to make that individual decision. I think a more pointed way of doing that, and it's what we're trying to achieve, I think, with a more complete assessment, is the ability to ask the question do you believe that you can objectively assess the evidence in making a decision to vote on this specific topic?

And the disclosure only brings that question up, and then ultimately I think the staff and the Chair, talking to the individual member have to make that decision about I think maybe you're conflicted here, and perhaps you shouldn't vote on the topic versus what happens most often is we need your expertise as long as you believe you can be objective, non-biased, and even if the evidence didn't support your current view, be able to vote one way or the other, either for or against a topic or

another vote that would be free of your, your know, personal biases, or professional and intellectual interests.

So that's what we're really trying to get at, and so there's a process behind it. It rarely in my experience, it rarely elevates to the level of asking someone to recuse themselves, unless there's a direct financial interest, or you would actually answer the question I believe this doesn't work, so I cannot vote for it.

Or, I believe this does work, and therefore I couldn't vote against it, and actually having to answer that question is, I think, useful. It does, I wanted to say it brings up issues for -- so what if the Chair is conflicted, so then it falls to staff. So I work as the Chief Medical Officer half-time for the State of Colorado.

The Health Department runs the newborn screening program. There are other state agencies involved with funding the care after a condition is added to the RUSP, and so I would have to tell HRSA I have a potential conflict from a professional standpoint because I have the interest and my state in mind when talking about these conditions.

And then staff here would have to say well Ned, do you think you can objectively review the

evidence for adding, let's say Krabbe, knowing what the direct costs to the State of Colorado would be in terms of screening, referral for treatment, confirmatory testing, and the treatment through the course of the disease while the patient is covered by say Medicaid.

So that's a potential conflict that they would have to make -- to call for, and they would have to ask, and they will ask me specifically do I think I can make that decision. Sue Berry?

DR. BERRY: Sue Berry from the SIMD. I noticed that with regard to organizational reps there was a comment about a percent of budget, or something like that. I presume that means the organization's budget?

DR. CALONGE: Yes.

DR. BERRY: In that. And it makes sense and is understandable. The organizational representatives come with their own things that would be potentially conflicts, and not necessarily related to their organizational representation. Is there a way to think a little bit about that, or consider that as a concern? You know, I think that is a potential that we need to recognize in some way. I'm not sure exactly how to do that because we're not just speaking for our representative, but we are

speaking for ourselves.

We're speaking for our organizations, and that's the primary reason we're doing -- we're here, but we have our own agendas and biases as well.

DR. CALONGE: Well, I appreciate that comment, Sue. And so, the issue would be disclosure only because we aren't -- there aren't actions that are associated with organizational reps because you're not taking votes, you're just participating. But I guess I would throw that open to the rest of the group and say do we want additional disclosures for organizational representatives where they could talk about their potential financial professional business, and intellectual conflict, or I like Shawn's word, "dualities".

So while you're thinking about that, I think we'll be thinking about how to work that. I'd like to turn to Natasha.

MS. BONHOMME: Thank you, Natasha Bonhomme, Board rep. Can you speak a bit to when I think this is maybe slide 5 or so, when speaking about financial interest and receiving research grants, that federal grants and nonprofit research grants were excluded from that? Just a little bit about why those are not included in the list. Is there something special or particular about them, or about proprietary and

business, private business grants just?

DR. CALONGE: Yes. So, great question. It's almost like you were in previous rooms. This is a point that was discussed actually quite a bit at both the USPSTF and the community guide. And the agreement was made that because federal grants are peer reviewed with a very transparent, maybe not transparent, but a very well-defined process about how they're reviewed within the confines of the RFP that gave rise to the federal grants, that they were less likely, and oh by the way, they are grants that are given to an institution, not an individual, that the feeling of the researchers were that these shouldn't count as conflicts of interest, whereas if a pharmaceutical company, for example, or a device company, or some other group gave you a grant that it's different in that there's a proprietary interest in how those grants -- how those projects come out.

Often, if a grant is given by a business, and it is found to not be effective, those grants -- those results might not even be reported because it's not a federal grant. So there was that separation made, and I think at the end of the day the leadership at CDC, and the legal advisers to the agency agreed that federal grants didn't need to be included.

MS. BONHOMME: Thank you. I think that's really helpful. And I think that's just maybe something to track because I know sometimes in, you know, every contract and every grant sometimes has fine print, and fine lines, so that just may be something to as you decide to implement this to monitor that, especially on nonprofit side, since there are lots of different types of nonprofits, or lots of different types of agencies, but I really appreciate the discussion.

DR. CALONGE: Thank you, Natasha. Bob?

DR. OSTRANDER: I just want to chime in on Sue Berry's comment again, and I agree with her. It looked to me like from your framework for the org reps that the main disclosure was going to be to the Committee members. And I think probably in addition to disclosing their organizations, the funding stream that the individual representatives' personal interest in things that might make money, or lose money based on the Committee's decision, probably should be disclosed, so the Committee members know that because hopefully the Committee members are taking our testimony into account with their decisions.

And again, since you're not restricting, it's fine, but in the name of transparency I think if

the individual who's speaking, not just as a representative of their organization, but the individual who's speaking tends to make or lose financial gain. Don't make it as wide and broad. You shouldn't do that it's going to make everything so complicated.

But I think personally it stands to gain or lose money may not be based on a decision, I think the Committee members should know that.

DR. CALONGE: I appreciate that, Bob, and I didn't want to be -- we didn't want to overstep given that its, you know, the organizational reps for the Advisory Committee here are different than non-member representatives for like the Advisory Committee on Immunization Practices, where most of them were automatically conflicted.

And they have a different role on the Committee, and our role is to try to be inclusive of those initial comments. So, perhaps what I would propose is that we sever that part of the proposal, but allow me to work more closely with organizational reps to design a disclosure system that was agreeable to you as a group, recognizing that there isn't a decision to take action to not let you make comments.

And I would be happy to do that. I wanted to make sure I didn't overstep, and since I didn't

ask organizational reps what would be good, I think it would be helpful. Some organizational reps like our friends, like Lieutenant Colonel Hogue, where I think it's less of an issue.

But I think having everyone go through the same process is something I would be happy to do, and work out with all of you because I think it is useful for the public to know who's speaking, and from what perspective. I really appreciate that, so I will circle back with you all, and Shawn, you put your hand down, so?

DR. MCCANDLESS: I just want to emphasize that I think Bob said this, and others have said it, but to emphasize, I think transparency is the issue that we're all influencing each other, and therefore we all need to know sort of what are the influences on each of us that are influencing how we influence each other. And so, it's more about transparency than about conflict.

DR. CALONGE: Yeah. I agree. 100 percent I agree. The conflicts are easy ones here, kind of directly make money. That's the easiest one in the world, so the other ones are more nuanced. Jennifer?

DR. KWON: And just to follow-up on that. I don't remember what form it was that I filled out, but there was also somebody at HRSA who looked at my

CV and commented on what they thought was an omission on my conflict form. And I thought that was actually very helpful as well because what I explained was that MDA and PPMD do give my institution money as part of being a certified center, a certified MDA and also PPMD center.

And that would look unusual if it weren't for the fact that it's pretty much a universal practice. Most pediatric neuromuscular programs of a certain size get both MDA and PPMD funding for their multi-disciplinary clinic activities, to both it provides a small amount of support, et cetera.

And I didn't know if there was going to be any comparison for gaps in the CV. I don't even know who did that, but it was an interesting thing to be presented with because I hadn't even really thought about that as a potential conflict because it's just so much of how we practice.

DR. CALONGE: Yeah. Great comment and question. So, the CPSTF does require an updated CV every year. I did not include that because I honestly was a little worried about HRSA staff reviewing 15 CVs on an annual basis, looking for the margins of where funding might come from. So it was a specific omission, at least at this time.

I do think, I don't know, whether beyond

the initial CV, whether the annual OGE process asks for another CV because I don't -- yeah, we don't. We just do it at the onset. I think even the CPSTF decided to do it every two years because we felt that you had to keep your CV up to date at least every two years for most institutions.

I'm wondering if we could consider that as something we could look at a later date. Debra?

DR. FREEDENBERG: I was just going to comment on the organizational reps. Those of us that are representing larger entities with multiple interests. You know, I do not know everything the AAP does, and where their funding comes from, and where it's going to. And nor do I expect to, nor do I want to, to be quite honest.

But I could not, you know, make a statement that AAP has no interest in that because I don't know exactly, you know, where their funding comes from, and there are large parts of it that I know nothing about. I mean I know this little area, but that's pretty much it. And so, I mean I'm sure you understand that.

DR. CALONGE: Yes.

DR. FREEDENBERG: With the larger organizations there are multiple interests and multiple folks.

DR. CALONGE: Yes. Well, and there's always I think the forms, I'm trying to remember. There's always this to the best of your knowledge. So what we want is like an earnest approach to the best of your knowledge. And if you don't know then you don't know.

The only place that's just so people are aware of where fines have been levied and lawsuits have been filed, to my knowledge, have all been in the financial disclosure area. That's where, and so I'm telling you all as individuals, as academicians, as people that work in the field, that it actually is a good idea to be as explicit and complete as possible in listing potential, financial interests because there have been institutions and individuals who have been fined or gone to court because of that.

And I only know that because whenever I start these dialogues, people drag all that up, so. So, yes, to the best of your knowledge.

DR. FREEDENBERG: Okay. Thank you.

DR. CALONGE: Molly?

DR. MINEAR: Just a quick question. So the intention is that we would be filing these disclosures. Would those disclosures then be made public, regardless of whether or not they result in an action?

DR. CALONGE: Right. Great question. So, hmm, at least the answer, so it's going to be a two-part answer. For Committee members, the answer is no. So, if one of the actions is it has to be disclosed publicly, so that would be a potential action. But most of these would be noted, and no action including disclosure would occur.

The idea is to try to keep the confidentiality about individuals and individuals like investments confidential. And so, let's say, I don't know, you invested in one of the companies who's working hard to create new gene therapies for inheritable diseases. The fact that you are invested in them would be reported. The Committee might choose to say okay, you need to be recused from this.

And the way it would be announced is Dr. Calonge is being recused because of a financial interest. That's it. Okay? Yes. We do fully intend to keep the details about personal information confidential.

DR. MINEAR: What about disclosures that might not result in the need for a public announcement, like they, you know, don't rise to the level of meaning something like that, but they -- would the Committee members have an interest in knowing what those are for everyone else on the

Committee?

DR. CALONGE: Yes. And the way that's been handled, and not in detail we've completed flushed out. But a conflict that didn't need to be publicly announced would be messaged to the rest of the Committee. So in the CPSTF, which is not a FACA, there's a pre-meeting where all of those are discussed and presented.

And then all we do in public is say these were discussed, and no actions were taken. Given the transparency required for a FACA, we haven't quite figured out how to do that yet, so that's something I would need to go back to the lawyers to discuss. Great point. It's almost like you've been in desk as before. Natasha?

MS. BONHOMME: Natasha Bonhomme, org rep. Two questions, if I can remember them. I guess one comment, and one's a comment. For federal grants there are some federal grants that do have the potential to lead to profit, such as through patenting and having those dollars go back to universities. I don't know if that is taken into consideration, since those patents probably go, and the money from that part of the university that would go back to either that same institution or center, that the representative is there for.

So I don't know if that came up in the discussions, or it would. And then my question is, I don't know if on the other FACAs or committees, even if you don't report back out specifically why someone wasn't able to participate in the discussion, is there an annual disclosure, or biannual? I don't know. A reason why in terms of what to not tie to a particular person, but an example of why someone was unable to participate in that discussion.

Again, since the purpose of this is transparency out to the public, this is a space that a lot of people are fuzzy on. I wonder if any of the Committees you've talked about have done that. Again, not to highlight the person, but just to show these are the types of conflicts, or activities that have come up that the Committee has had to adjust for.

DR. CALONGE: I don't know that groups -- the second answer first. I don't know of any groups who have done that. Certainly one could talk about issues. I know the CDC keeps all of those forms, and then the most they'd make public is conflicts were discussed and no actions were taken, or conflicts were discussed and an action was taken, so the details are not made public.

The OGE 450 contents aren't made public

either, so those -- there must be a confidentiality clause associated with being an SGE, completing an OGE 450, gosh I love all these acronyms numbers, but it is something I can look a little bit farther into. And I suppose to your other issue, is we could say you don't have to report federal grants unless there is an opportunity through a mechanism for that grant to end in financial reimbursement directly to the researcher, or the researcher's family.

That would be an addition to what I've seen in the past, but I understand that that can be possible. So my proposal to move us ahead if we could is to separate out the organizational representative part of the proposal. Specifically add language around federal grants to say unless there is opportunity, the federal grant will result in direct financial benefit to the individual, and with those changes could -- adding perhaps the word duality, to the duality and conflict of interest to capture that concept that Shawn put forward.

With those changes, is anyone willing to make a motion?

DR. PHORNPHUTKUL: I'll make a motion.

DR. CALONGE: Thank you, Chanika. Is there a second?

DR. KWON: I'll second.

DR. CALONGE: Thank you, Dr. Kwon, and the members please, oh --

DR. MCCANDLESS: Sorry Ned, this is Shawn McCandless. I'm wondering if we could table the motion until tomorrow, and give us an opportunity to read the updated language?

DR. CALONGE: You bet.

DR. MCCANDLESS: Thank you.

DR. CALONGE: So, as long as the nominator and seconder is okay with giving us a chance to make a change, that would be great.

DR. PHORNPHUTKUL: That's fine.

DR. CALONGE: Okay. And I will just checking. I'm pretty sure that we put in the Federal Registry a notice that we would vote. Sorry. We're just checking real quick. I might have been -- I thought we had done that. I thought we were voting for tomorrow, but we'll check in time for tomorrow. That will be great.

Introduction to Listening Session: Considerations for Nomination and Review Processes

DR. CALONGE: Okay. Let's see. I guess I need the screen to be pinned back so I can see myself talk, and I don't know how to do that. So, I want to introduce the listening sessions that are coming up

during the -- oh, let's go to the slides. During the calendar year we've had several Committee discussions and comments on our process for nominating and reviewing conditions.

We initially considered the creation of an ad hoc topic group to review the current process and provide recommendations. We had an inspiring and overwhelming interest from Committee members, organizational reps and the public to participate in ad hoc topic group on the nomination review process, and decided that listening sessions would give an opportunity to solicit feedback from this larger group of stakeholders.

Prior to providing more background on the topics, I wanted to emphasize this will not be the only chance you have to share feedback on this topic. This is the first of probably or possibly, sorry, several listening sessions. And we could also do a Federal Registry process to solicit written feedback and comments as well.

We want a true, broad level of feedback to ensure that there are several opportunities for stakeholders to contribute their thoughts and suggestions. The nomination process. We currently encourage a multi-disciplinary team, comprised of researchers, individuals with lived experiences,

advocacy organizations, states and so on, to develop and submit a nomination package for the Advisory Committee to consider specific conditions for inclusion on the RUSP.

In practice this creates a substantial burden on groups that may not have the resources to gather all the required information. Furthermore, in the near future with advances in genomic sequencing, new treatments and other approaches, hundreds of conditions might be considered for universal screening.

You may recall that Dr. Kemper presented some options using a point system on how the Committee should prioritize nomination and prioritization based on work that the ERG did. There was a lot of discussion addressing core issues about how best for the Committee to operational this approach.

And Dr. Kemper also presented on how other national evidence-based groups do reviews. Provisions to the NMP process should consider the best balance, introducing the burden on the nominators, but including they have -- ensuring they have sufficient input in the process, and identifying the information most needed for the Committee to make our evidence-based decisions.

We want to be sure that the Committee's condition review process is sufficient, can address multiple nominations at once, and preserves and elevates stakeholder voice. So the questions we will be asking regarding the nomination process are as follows.

First, should the acting consider other approaches to the nomination process that could reduce the burden on nominators, and increase the role of the Advisory Committee and federal agencies to provide support, and the needed information.

Second, if the nomination process changes, how can we ensure that advocates and individuals with lived experience voices are included in the nomination process? And third, are there other gaps or concerns regarding the nomination package that you'd like to share?

So, let's turn next to the evidence-based review process. We would also like to take a critical review at our process here. We've identified the decision matrix tool, and potential updates to the tool, but we want broader feedback for the concepts related, especially to the magnitude of benefit and harm.

The criteria for inclusion on RUSP is based on published evidence that benefits outweigh harms,

and the certainty that the evidence available in the peer reviewed literature is sufficient to support that assessment of magnitude. Historically, we apply these criteria to elements that focus on the benefits and harms to the individual child.

Evidence regarding other elements, such as benefits to the family, or societal considerations such as a financial cost, or public health opportunity costs, have not been considered. Furthermore, when making recommendations, the Advisory Committee does not have a way to weigh the benefits to one population of children against the potential harms to another population.

So the questions we're going to ask during the evidence-based reviews process are on the screen now. How should the Committee consider benefits associated with screening, given these different perspectives, like the child, the family, the clinician, the public health system and society?

Similarly, how should the Committee consider harms associated with screening, again given the different perspectives? Number three, how should the Committee balance benefits and harms to come to a decision about net benefit? This is especially important when the currency of the harms, and the currency of the benefits may not be the same.

Four, how can the Committee consider the overall burden of potential illness that might be averted? Number five, how can uncertainly regarding screening outcomes be systematically considered, given the lack of data, especially around potential harms?

And number six, the issues of overall economic costs and opportunity costs are often unclear. How should the Committee consider these unmeasured costs, which are also likely to change over time? So those are the questions we propose we focus on. There's a lot there, a lot of meat, a lot of places for really important input, which is why we say again, this may not be the only time we do this.

But I'd now like to turn things over to Leticia, who will provide some instructions, but before I do that I think Jeff wanted to make a couple of comments.

DR. BOSCO: Yeah. This is primarily for our Advisory Committee members and organizational rep members who are assigned to each of the listening groups. So just some quick instructions. Each of the listening groups will have a person or volunteer who is facilitating the discussion.

They are not subject matter experts. Their job is just to facilitate the discussion, and make

sure that folks get a chance to participate. There may be times when your subject matter expertise may be necessary to ask qualifying questions, so your job is primarily in listening, these are listening sessions. But I may also be that if a comment comes from someone, and you're not quite clear in what they mean, we would love for you to ask a clarifying question because you will be helping us report out tomorrow morning, thank you.

DR. CALONGE: Now Leticia, can you tell us how we're going to do this?

COMMANDER MANNING: Okay. I have the instructions. So next slide please. When you all registered, many of you all selected a group, but we do understand that your feelings may have changed since then, and you may want to participate in a different group.

So as a reminder, if you're logging on through Zoom, you'll have the meeting ID and passcode. You can see that here on the screen. You can also access the Zoom links at ACHDNCmeetings.org/listening, and that will give you the specific link for each of the different groups.

I want to just provide a little bit more information for folks. Each category of questions, so the nomination portion, and then the

evidence-based review criteria portion, we're allotting 45 minutes for each discussion, but we are very much aware that there are a lot of questions, a lot of participants, and that you may not have sufficient time to get through every question, and that is okay.

There will be other opportunities for you to share your feedback. We'll be issuing a Federal Register notice to solicit written feedback, and there will also be opportunities, depending on what the updates are for tomorrow, to have other listening sessions and other opportunities to share.

The rooms will be open in about five minutes, and the sessions will begin at 2:15 Eastern Standard Time.

DR. CALONGE: Thanks. And let me just thank you all ahead of time for your participation in these listening sessions. I know they're going to be of critical importance in how we move forward with the Committee, our decision process, and we couldn't do it without this input.

So with that I'm going to close this combined session for all of us, and we're going to try to hop in and out of some of the separate groups, and then we'll definitely see you all tomorrow at 9:30 when we reconvene the entire group. So thank

you. All right.

(Whereupon at 2:05 p.m. the Meeting was adjourned, to reconvene tomorrow at 9:30 a.m..)