The Advisory Committee on

Heritable Disorders in Newborns and Children

Virtual Meeting

9:30 a.m. until 2:00 p.m.

Friday, February 10, 2023

Attended via Zoom Webinar

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Reported by C. ANN LORMAN

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DAY 2

WELCOME

NED CALONGE: Good morning. I want to welcome everyone back, day two of the Advisory Committee for Heritable Disorders in Newborns and Children meeting.

Today we have another busy agenda. We're going to start with an update from the Prioritization and Capacity Workgroup. Followed by that we'll have public comment and then reports from the workgroups that convened yesterday.

Following lunch, I will provide the nomination summary for Duchenne's muscular dystrophy. Concluding this discussion, there will be a vote of whether to move DMD to full evidence review.

Finally, we will hear from three HRSA Interoperability Program grantees.

At this time, I'd like to turn it over to Leticia for roll call. Concluding roll call, I have a comment, and then I will turn it

over to Dr. Kemper for the presentation on prioritization and capacity.

So, Leticia, if you could do the roll call.

LETICIA MANNING: Sure. Thank you, Dr. Calonge.

ROLL CALL

LETICIA MANNING: I begin with the Committee members. From Agency for Health Care Research and Quality, Kamila Mistry.

KAMILA MISTRY: Yeah, you got it there.

LETICIA MANNING: I've been practicing.

Kyle Brothers.

KYLE BROTHERS: Here.

LETICIA MANNING: Michele Caggana.

MICHELE CAGGANA: I'm here.

LETICIA MANNING: Ned Calonge.

NED CALONGE: I am here.

LETICIA MANNING: Carla Cuthbert.

(No audible response)

LETICIA MANNING: Jannine Cody.
JANNINE CODY: I'm here.
LETICIA MANNING: Jane DeLuca.
JANE DeLUCA: Here.
LETICIA MANNING: Kellie Kelm.
(No audible response)
LETICIA MANNING: Michael Warren.
MICHAEL WARREN: Here.
LETICIA MANNING: Jennifer Kwon.
JENNIFER KWON: Here.
LETICIA MANNING: Ash Lal.
ASHUTOSH LAL: Here.
LETICIA MANNING: Shawn McCandless.
SHAWN McCANDLESS: Here.
LETICIA MANNING: From the National Institutes of Health, Melissa Parisi.
MELISSA PARISI: Here.
LETICIA MANNING: Chanika Phornphutkul.
CHANIKA PHORNPHUTKUL: Here.
LETICIA MANNING: And now for the org reps.

For the American Academy of Family Physicians, Robert Ostrander.

ROBERT OSTRANDER: Here.

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

DEBRA FREEDENBERG: Here.

LETICIA MANNING: American College of Medical Genetics and Genomics.

ROBERT BEST: Bob Best, here.

LETICIA MANNING: Okay. Thank you. Sorry.

The American College of Obstetricians and Gynecologists.

(No audible response)

LETICIA MANNING: Association of Maternal and Child Health Programs, Karin Downs.

KARIN DOWNS: I'm here.

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

SUSAN TANKSLEY: I'm here.

LETICIA MANNING: From the

Association of State and Territorial Health Officials, Scott Shone.

SCOTT SHONE: I'm here.

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

(No audible response)

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

MARGIE REAM: Here.

LETICIA MANNING: From the Department of Defense, Lt. Col. Hogue.

(No audible response)

LETICIA MANNING: From the Genetic Alliance, Natasha Bonhomme.

(No audible response)

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

(No audible response)

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

CATE WALSH VOCKLEY: I'm here.

LETICIA MANNING: And from the Society for Inherited Metabolic Disorders, Gerald Berry.

GERALD BERRY: I am here.

LETICIA MANNING: Thank you.

And that concludes the roll call.

NED CALONGE: Thank you, Leticia.

OPENING REMARKS AND COMMITTEE BUSINESS

NED CALONGE: We had a question that came up after the meeting adjourned yesterday regarding clarification of the vote. I wanted to just go through that real quickly.

So, the motion, if you recall, was to recommend to the Secretary to add Krabbe to the RUSP. The vote, and we went back and double-checked it, was seven to seven. The Advisory Committee follows Robert's Rules of Order. And without a majority vote, a motion fails. So, that's the clarification of the outcome of the vote yesterday.

And I appreciate the question and

opportunity to review and clarify that.

With that, I'd like to move ahead in the agenda and turn things over to Dr. Kemper, who is still the Division Chief, Primary Care Pediatrics, at Nationwide Children's Hospital, and Professor of Pediatrics at the Ohio State University College of Medicine.

INTERIM WORKGROUP UPDATE: PRIORITIZATION AND CAPACITY WORKGROUP

ALEX KEMPER: So, thank you very much, Dr. Calonge.

What I'm going to do over the next little bit is talk about a project that we've been working on to help prioritize nominations for the recommended newborn screening panel, or the RUSP.

Next slide, please.

(Slide)

ALEX KEMPER: So, this is just a list of people that are working on this particular project.

Next slide, please.

(Slide)

FEMALE VOICE: Is someone's volume on?

(Pause)

ALEX KEMPER: Yes.

As always -- you can go back to the previous slide, please.

(Slide)

ALEX KEMPER: As always, we have a workgroup --

(Inaudible interjection)

(Pause)

ALEX KEMPER: Yeah. I hope you can hear me okay.

So, individuals who can provide technical guidance and weigh in with their expertise.

Next slide, please.

(Slide)

ALEX KEMPER: So, by way of background, there's a potential increase in the number of nominated conditions that could come to

the Advisory Committee. This could be due to advances in newborn screening technology. For example, additional conditions that could be multiplexed together in screening, or even genetic sequencing as the advisory community has discussed in the past.

There are also treatment advances, including gene therapy and novel targeted therapies that could increase the number of conditions that might be considered for the RUSP.

As previously discussed at Advisory Committee meetings, there have been concerns about the limited capacity to meet demands of the potential increase in the number of nominated conditions.

Next slide, please.

(Slide)

ALEX KEMPER: So, I think it helps as we get into this conversation to just review the cadence, the current pace of topics that have been considered.

And I'll just leave this slide here

up for a second so that you all can get a sense of the number of conditions that have come in and the timeline from when the nomination was first submitted to when it was referred to evidence review, and then when a recommendation was made.

Next slide, please.

(Slide)

ALEX KEMPER: So, please advance again.

(Slide)

ALEX KEMPER: So, in terms of this particular project, at the February Committee meeting there was discussion about the capacity to review conditions.

Please advance.

(Slide)

ALEX KEMPER: And by way of background, the Nomination and Prioritization Workgroup has previously developed criteria to review submitted nomination packages. But it's clear that the Nomination and Prioritization Workgroup has a finite capacity.

In addition, the Advisory Committee has restrictions on the number of reviews that can be considered simultaneously -- that is, at any particular given time. And the Advisory Committee does not have criteria for defining how to prioritize multiple simultaneously nominated conditions.

So, determining which condition should begin first while others wait.

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(Slide)

ALEX KEMPER: I want to highlight, though, that has not been a concern yet. The Advisory Committee has never been in the position of having to prioritize one condition over another for evidence review.

Next slide, please.

(Slide)

ALEX KEMPER: But to begin to prepare for that potential, a workgroup with Committee members past and present, as you previously saw, were convened to develop criteria and a process

for prioritizing the review of nomination packages. And this is going to also include input from stakeholders.

Next slide, please.

(Slide)

ALEX KEMPER: So, I want to frame things by just pointing out that prioritization is common. So, Dr. Calonge spoke yesterday about the US Preventive Services Task Force. And I'd just like to build on that and talk about the taskforce approach to prioritization.

So, what the US Preventive Service Task Force does is that nominated conditions are reviewed to determine if they are in scope and if they are a new topic. And if they are in scope and they are a new topic, then it begins a process for prioritization.

That prioritization process includes a request from feedback on all active and potentially new topics, which is sent to task force members and partner organizations. And then they're asked to vote on whether the condition is

high, moderate, or low priority for review in the next 12 to 18 months.

And then there's a Topic Prioritization Workgroup that assigns a tentative priority category. And then the full task force votes on that priority category. And that way, the cadence of competing topics can be determined.

Next slide, please.

(Slide)

ALEX KEMPER: In terms of key points --

Next slide.

(Slide)

ALEX KEMPER: As I hope I've pointed out, prioritization is about cadence. The idea of prioritization is it's not used to stop a condition from moving forward to evidence review.

If it's recommended by the usual Nomination and Prioritization Workgroup methods -- that is, if the Nomination and Prioritization Workgroup determines that there is sufficient evidence to move forward, the condition will still

move forward. Again, the prioritization is about timing.

Next slide, please.

(Slide)

ALEX KEMPER: And when prioritization is needed, the process should be transparent to all stakeholders -- that is, member of the Advisory Committee as well as the public, and everyone else invested in newborn screening.

Next slide.

(Slide)

ALEX KEMPER: And so, thus far what we've done is we've pointed out the key principles for prioritization.

The goal of the Advisory Committee work, and this translates to the Nomination and Prioritization Workgroup, is to maximize public health benefit, taking into account issues like prevalence, expectation of benefit for newborn screening, potential harms, screening test validity, the reduction of inequities, the ability to implement comprehensive screening, and to

ensure that the Advisory Committee still has a balanced portfolio of conditions.

And when the workgroup calls, there's been a discussion about whether prioritization should involve a qualitative assessment to a more formal point system. And at our most recent meeting, there was general consensus to move forward to a more formal point system, which helps both with transparency and with making what might be difficult decisions.

And as a matter of fact, we look back at the point system that was used when the RUSP was initially formed, to think about categories that would fall into such a point system.

Next slide, please.

(Slide)

ALEX KEMPER: So, there are additional benefits to the prioritization process other than just cadence. So, it can be used to help further structure and provide clarity about the nomination process. That is one of the big, key elements that are needed from nominators.

Next slide, please.

(Slide)

ALEX KEMPER: And in terms of the potential process, in the event that there has to be prioritization -- and again, this hasn't been an issue in the past -- the Nomination and Prioritization Workgroup would make recommendations to the Advisory Committee based on the process that I just described, which is still in development.

And that the Nomination and Prioritization Workgroup would regularly present the list for conditions that had been nominated, but not yet prioritized for review, again to make sure that there is transparency and equity in how the process works.

Next slide, please.

(Slide)

ALEX KEMPER: So, with that I'd like to end there and open things up to questions about what this group is doing.

NED CALONGE: Thanks, Alex, very

much.

I'd like to start with questions from Committee members, and then we'll turn to questions from org groups.

Seeing no Committee member hands, Robert, I'll start with you.

ROBERT BEST: Thank you, Ned, and great summary, Alex.

I had some questions about the ethics. I'm surprised Kyle hasn't jumped in and just made all my points or answer them before I ask them.

The one is sort of deciding that the greatest public health good is the ethical right answer when we have issues of equity. And I'm not saying it's right or wrong, but I simply have to understand that that is an issue of equity.

You happen to have a rare disease, you're much less likely to be nominated and have your condition screened for because it's not as common as other people. And I understand that that needs to be done, but we need to be clear

that that's an ethical decision that we've made if that's the choice we make.

I have concerns that factors will enter into the prioritization that are not necessarily in that list unless we make them overt to consider. And I think, you know, we have to consider the strength of the advocacy group. And again, this came out terrible the last time I said it; I'm not sure how to say it.

But you have a prominent person who's passionate about something, I fear that's going to push someone up the prioritization for less objective reasons. It's because they're there. And again, it's not a problem that there's a solution for, necessarily. But if we're not cognizant of it and it's not overt, it will affect our transparency.

And I'm going to chime in here with -- I've probably raised here a bunch of times and when we talk about DMD later. But I think we have to be careful about the notion of choosing a formal point system to trick ourselves into

thinking that our decisions are more objective or more valid because we've done something quantitative when it really isn't something quantifiable.

And I think, honestly, and this is something I've been studying since college, I think honestly it is a source of epistemological, if that's the right way you say the word, error to assign point values to make us feel better, feel more objective. Just because something has that number doesn't mean it's more real than if it has the qualitative value to it.

So, those are kind of my uneasinesses (sic) as we move forward with this.

ALEX KEMPER: Let me respond by saying I agree with you, right? You can put a number on something and give it a false precision. And I think the value of a point system, though, is it at least communicates what people are thinking about.

But how do you rate those different categories? Like it could change things, right?

So, where, you know, how many points various things get.

So, what our next step was, I was going to go back to some of the other conditions that the Advisory Committee has done and try different point systems and just test it to see where things happen. And then also come out with hypothetical conditions that, you know, sort of break the system, you know, that sort of push things to where it might not work.

Because I think that that kind of work added time would just help us identify where the problems are. So, I agree with everything you just said.

The only other thing I'd like to highlight, though is that -- but again, it hasn't been a problem in terms of having prioritized things in the past. And I don't know if it ever is or not. And all of this process is not to stop something from moving forward. So, I just wanted to understand those things.

But your points are well taken. And,

you know, I'd invite you after we develop these scenarios if you want to play around with it, certainly you're welcome to do so as well. I would value that.

ROBERT BEST: Can we agree that maybe points systems are a tool and not a rule? I even find that to be a little bit of an issue with our matrix. You know, I think tool and not rule is a good way to think of that.

ALEX KEMPER: Yeah. I'll certainly bring that up with everyone else. But your point is well taken.

NED CALONGE: Jane.

JANE DeLUCA: Thank you. And thanks for your presentation, Alex.

I just had two questions. One is that the recent reviews for MPS II and GAMT ran very close to each other. So, I wonder if you could speak to that experience as being not quite reaching the threshold of, oops, you know, how do we prioritize something here?

And the thing that I wanted to ask,

and just tell me if I'm on the wrong track here, is when we're talking about looking at things, different disorders for review, there is this process with many stages. So, you could be talking about something that's overlapping at different stages, something that's more complete or less complete.

So, how do you explain that? You don't necessarily have two things coming in at the same time.

ALEX KEMPER: Well, let me rephrase your question a little bit to make sure -- I may be getting your question wrong. So, first of all, thus far, you know, and you're right, we had MPS II and GAMT ran, you know, kind of overlapping and that kind of thing, we had plenty of capacity to process.

We're fine. Things followed along our manuals of procedures, the ways that we go. So, that there were no concerns there.

I think that, again, some of the reasons we might prioritize are things outside of

what we as a group do right. So, testing issues, of the Advisory Committee's ability to consider multiple conditions in a kind of thoughtful way, and those sorts of things.

So, the decision about the capacity and the number of conditions that could be done simultaneously are ones that fall to the Advisory Committee itself, and to HRSA, which funds the work of the evidence review. But it's not something that's a decision that I make.

Does that answer your question?

(No audible response)

NED CALONGE: Natasha.

NATASHA BONHOMME: Thanks. Natasha Bonhomme, Genetic Alliance.

Bob said a lot of what I was thinking, so thank you for getting that already out there.

But two items. One is the chart that you put up, and I'm looking for the name of it. The Current Case chart, will that be posted on the Advisory Committee website or anything? I think

that's a lot of really great information that could help part of this process be more transparent in terms of where we've been and so why this conversation is coming up.

I don't know if you want to --

(Crosstalk)

ALEX KEMPER: I know our slides get posted, and certainly I can talk with HRSA about getting there. And I'd separately be happy to send that table to you if it would be useful for the work you do.

NATASHA BONHOMME: Right. Right. No, I actually more so mean being transparent to the public. So, not everyone wants to go through all of the -- how big is the binder, 100 or so pages? But you know, if there were anything about this, an initiative of the Committee or in your work, maybe a section on the website would be helpful to have that be transparent.

And that kind of leads to my second point of, depending upon how this concept goes, I would just really encourage that whenever we get

to that end point, whatever that looks like, that there is some companion language that can be available for the public to understand that and to really get a clear understanding of, what do these numbers mean? Where are things weighted?

As I said earlier, I think even with the progression of the matrix over the many years, there's still confusion about, what does this mean versus that? And so, I would hate to miss the opportunity to clarify that in this process.

ALEX KEMPER: Excellent suggestions. And we will definitely do that.

NED CALONGE: Bob.

ROBERT OSTRANDER: Yeah, thank you.

So, just two brief comments and also a short question. So, one is, you know, one of the problems I think in decision-making in medicine generally is the reliance on expert opinion, expert systems. So, you know, the concern about false precision with scoring systems really comes to mind there. So, I think that just a careful adherence to an evidence-based process

is really essential.

And I think it's really easy for us, as experts, to miss -- you know, to sort of build into the assumptions so it's almost like a tautology, right? We have certain assumptions; we're not always aware of them. And so, if we don't adhere strictly to evidence, I think there's this problem that we might just prove our assumptions in our scoring system.

So, that's just a caution.

Second was just in terms of the prioritization of conditions. So, I think it's really important to be careful not to allow an administrative process to override the intent for this to be determined more publicly. And I think that's -- just be careful of that.

Third is just a question. And I wondered, there was mention of a balanced portfolio of conditions. And I wonder if you would just take a minute and be a little bit more explicit about what that might mean.

ALEX KEMPER: Yes. So, again, this

is all work in progress.

You disappeared. Oh, there you are. You moved on my menu, my bingo card.

So, the other Committees like the US Preventive Service Task Force try to make sure that it's looking across the different types of conditions that can be included. So, pediatric-to-adult, you know, heart disease, pulmonary disease, you know, those kinds of things.

And the notion of the balanced portfolio was to think about those conditions that you can imagine in the future that might be added to the existing systems, where there might be -- the technology might be an incremental benefit.

And the thinking was that if you just always focused on those kinds of things, you might miss the opportunity to think about a new technology or a new platform or a new point of care, that kind of thing.

And so again, I can't comment on how that would be weighted. But the idea being that it would be an opportunity to make sure that

thinking outside the box still occurred.

ROBERT OSTRANDER: Yeah. Thanks very much, Alex.

ALEX KEMPER: Did that make sense? And again, it's not the intention of this prioritization process to put the stop on any condition from moving forward. It's just a matter -- you know, the particular cadence. And at the risk of repeating myself, again it hasn't been a problem in the past, so this is mostly thinking about making sure that we don't run into problems in the future.

ROBERT OSTRANDER: And I'll just say, as far as intentionality, I mean, I think the intentions are always great. And we still have sort of run aground in some ways. Medicine, generally, with the use of experts, expert opinion systems. So, just a caution, that's all.

ALEX KEMPER: No, I 100 percent agree.

NED CALONGE: The slide, Natasha, that Alex presented that you asked about came from

information that is already posted on the website. And we'll make sure we send that URL along so that everyone kind of has access to it.

Michael, did you have a comment?

MALE VOICE: You're mute, Dr. Warren.

MICHAEL WARREN: I did, and Dr. Calonge just stole my thunder. I was going to say that. So, kudos to you for being always a step ahead. Thank you.

NED CALONGE: Well, I have to thank K.K. for helping me be so smart.

(Crosstalk)

ALEX KEMPER: We all have to thank K.K. for a lot of things, so I appreciate that shout-out to her.

NED CALONGE: Shawn.

SHAWN McCANDLESS: Thank you. Shawn McCandless, member.

I guess I'm thinking about what Dr. Ostrander was saying. And I feel like it's really important to point out or just to remind ourselves that this actually is a public health program and

we're screening all babies.

And so, I don't think it's wrong to make public health priorities, priorities. And if you have two -- you know, the advantage of the point system, recognizing that it's not perfect, but the advantage of having a point system is that you're forced to rank relative values in various areas, including -- and so you could end up with two conditions that are otherwise equally well represented. There's a good treatment for both.

There's many other factors that are very similar. And then if there is a need to prioritize, why would you not prioritize the more common condition that's going to save more lives than the less common condition?

So, I'm not sure I understand the concern.

ROBERT OSTRANDER: I agree completely. I just think when we're making ethical decisions, we need to realize that we're making an ethical decision and the consequences of it. I don't disagree at all. I mean, we have to

make decisions, and public health is indeed what this is.

But the problem is when you've got room for cognitive errors and things can be ethically murky, the decisions need to be made overtly and intentionally and not by default. And that was all I wanted to point out.

Because it does come up and it will come up from advocacy groups for rare conditions, that how come our children are just as sick and are just as important as those children? There are just more of them. You know, and we're certainly in an era where equity is on everybody's mind.

And again, I don't think the decision is wrong. I'm sorry if it came across that way because that was not my intention at all. All of my points really were that we needed to be cognitive of what we were doing and have that discussion open about whether use a point system or not, about if we choose based on disease prevalence and not just do that as an assumption.

So, I appreciate your comments and the opportunity to clarify because I did not want anybody to think that it was the wrong idea to do things based on prevalence.

SHAWN McCANDLESS: Thank you. And I also appreciate both you and Dr. Best bringing up this topic of cognitive bias and how it impacts expert opinion. That is something that I am very concerned about personally in many decision-making areas.

But I keep coming back to this idea of a point system because I think that the beauty of what is being proposed here is that it is -- it's more transparent than the system we currently have. It will be publicly available, and people will be able to understand going into the decision-making process how the decision will be made.

And they will be able to actually see, What were the components of the decision-making process that would allow people not only to understand decisions that were made, but to

monitor externally if there is something that's not quite right, if there is an over-emphasis on an expert opinion or something else?

That should become more apparent and more clear by the increased transparency of this system, which to Alex's good point probably is not -- it's probably not going to come up. But if it does, it's not going to be very often. And if it does delay something, it would be a delay probably of four months.

So, you know, points are well taken, but I just want to say that I think that this workgroup has been very thoughtful and intentional about this. And I think the proposal, when it's fully fleshed out, is going to be quite valuable.

NED CALONGE: Kyle.

KYLE BROTHERS: Yeah. I was just going to add some clarification from that perspective as an ethicist. I feel like when folks start bringing up ethics in this context, I have this obligation to respond because then like, what am I even here for, you know, if not?

So, just thinking about the association of the low frequencies and founder effects with the ancestry groups, it really becomes clear quickly that when conditions are associated with either low frequencies or founder effects that track with ancestry groups, that prioritizing exclusively on the basis of frequency, prevalence within the general US population, can cause ancestry group to be the primary driver of prioritization rather than the condition itself and can create systematic bias against conditions that are more common in ancestry groups that are less common, if that makes sense.

There are really great -- well, maybe not really great, but there are ways to deal with that. So, one strategy that we could use is to think about not using prevalence in all comers in the US population, but rather to consider prevalence within any particular population.

So, that if a condition is quite common in the particular ancestry group that is a

minority in the US, it would still receive a high priority on that basis and it would not require overall high prevalence on an average across the entire US population.

So, anyway, I fear I delved deep into genetics language there, but hopefully that makes sense.

NED CALONGE: Appreciate it, Kyle. Thanks. And you're here for more than just that piece.

Karin.

KARIN DOWNS: I wanted to completely agree with what Kyle just said. I was wondering in the goal of addressing equity whether there was any thought to actually including race and ethnicity in the prevalence of a particular disease or metabolic disorder.

Because I think to get towards equity, we would definitely need to do that rather than apply the prevalence to the whole population.

ALEX KEMPER: Yeah. And that's what we were thinking with that equity line there. We

just hadn't figured out exactly how to operationalize that.

KARIN DOWNS: What would the challenge be to operationalizing that?

ALEX KEMPER: Well, the same challenge as figuring out like what the point system would be and how delayed and that sort of thing.

KARIN DOWNS: Would it be a challenge of not having the racial/ethnic background of -- okay.

ALEX KEMPER: Yeah.

KARIN DOWNS: So, that is not consistently collected?

ALEX KEMPER: Well, I think the birth certificate. Well, so it's the goal of the prioritization process, it's going to build off of whatever we have from the nominators, right? So, we can't do, you know, like a separate full evidence review going -- you know, in order to prioritize.

So, again, I can imagine that we have

limited evidence. But to the degree that's available, we will do it. And what I can tell you anecdotally from having done a bunch of these evidence reviews is that there's often, you know, important gaps around what we know about prevalence of raw, let alone within certain groups.

So, you know, we'll just have to see.

NED CALONGE: Shawn.

SHAWN McCANDLESS: Two comments. One is related to what Kyle was talking about. I feel like there are many examples of genetic isolates or groups that are experiencing a founder effect where you have a sort of localized pattern of increased incidence of a particular disease. And I actually think that those situations are best handled locally.

I mean, this is not a national newborn screening program. This is a Committee that makes recommendations about what should be standard screening across the entire United States.

So, if you are in an area, for instance, where I used to work in Ohio where we had a high incidence of a population with certain conditions, there were ways to deal with that locally that were much more appropriate than forcing a national solution.

I do want to be careful too that we don't get too far away from the concept of -- we're really talking about a very specific action here, which is how to prioritize if we have multiple nominations coming in at once: Which is going to be addressed first? And I feel like we need to be careful not to get too far into the weeds about some of these other things.

That said, in response to something Karin said, you know, that Alex's point is well taken, that at the point of nomination and prioritization, it has nothing to do with what's on the newborn screening card. It's what's known about the condition in the medical literature, what's already known, what's in the nomination package.

That if we were going to start thinking about sort of how race and ethnicity and geographic origin impact things, I think another equally important and possibly more important question comes back to the difference of, which populations accrue the benefit of the screening program and what populations accrue the harms related to the program? And are they different? And is there any evidence that would suggest that there's a racial bias?

And I come back to some of the MPS conditions, where we know that there were higher rates of pseudodeficiency alleles that were not so well defined in the African American population that really raised the potential for that population to inappropriately suffer harms from a newborn screening program, while other populations that had higher incidences of the disease that would be screened for would actually accrue the benefits.

So, to my mind, that's something that we have to really continuously be careful about.

NED CALONGE: Thanks, Shawn.

Chanika.

CHANIKA PHORNPHUTKUL: Yes. So, I just want to emphasize that this is a screening to prioritize the project that we'll be moving forward. And this is not -- I also think that we should make it clear that the evidence-based review will be reviewed in detail. And it does not guarantee that whatever condition will be part of the newborn screening.

It's two separate processes. And I think sometimes people forget, especially if there's a lot of layers, a lot of things that have been put in place in order to get all the information.

So, I just want to make sure that we've made it clear that this is just prioritizing. But we're going to review. And we will have a review process, which there may be an outcome that is not what we thought. It would be inappropriate.

So, thank you.

ALEX KEMPER: Thank you for those comments.

NED CALONGE: Any other comments?

Alex, do you have any questions of us?

ALEX KEMPER: Just more to come. And as we trial different approaches, certainly I'll be reaching out to members of the Advisory Committee beyond our excellent working group.

NED CALONGE: I appreciate the discussion. I want to thank you all for your comments. And it will help move the work of that group forward.

I'd like to move on then, if we could, to our public comment period for today.

PUBLIC COMMENT

NED CALONGE: We received eight requests by individuals to provide oral public comments to the Committee. And I have an order for them and would like to start with Samantha Nikirk.

(Pause)

NED CALONGE: And, Samantha, I see your name and you're muted. There you are.

SAMANTHA NIKIRK: Very sorry. When I was promoted to panelist, I think it went out for a second there.

So, I'm here today to talk about my daughter, Evie. She is my second daughter, and she was born premature at 36 weeks.

Can you hear me?

NED CALONGE: Yes.

(Crosstalk)

SAMANTHA NIKIRK: When she was born, she had dark spots and purple bruising on her face that I thought were birthmarks. And aside from failing her initial hearing screen, which we were assured was most likely fluid trapped in her ears, she came home the next day. She was four pounds, ten ounces.

She was so small, in fact, that when her weight finally registered on the growth scale a month later, we had a little celebration in the

pediatrician's office. We didn't fully realize it at the time, but even then we knew we had to log all of her accomplishments.

When she was three months old at her follow-up ABR appointment, we received the news that she is deaf. We were told that the most likely cause of the hearing loss is genetic.

And after an odyssey of testing, which included sending the remnants of her dried blood spot from her newborn screening card across the country to the University of Washington, the cause of her hearing loss was identified as congenital cytomegalovirus, or CMV.

But because she was already three months old, the initial test they conducted to see if she had antibodies or CMV in her blood or CMV DNA in her urine were futile and necessitated the testing of her dried blood spot.

We learned that Evie had signs and symptoms of CMV at birth that were missed. The dark spots on her face were associated with congenital CMV in newborns and are a sign of

thrombocytopenia.

In combination with the fact that she was small for her gestational age, premature, has white matter injury, and referred on the newborn hearing screen bilaterally twice on two separate days, she could have been treated with antivirals at birth, which have been shown to help prevent hearing loss and developmental delays in children with congenital CMV.

However, she was diagnosed too late, as they are supposed to be started in the first 30 days of life. She was already four months old.

She's two-and-a-half years old now, and she has multiple lifelong disabilities that compromise her ability to walk, speak, and learn. She's done countless hours of many different therapies. She has global developmental delay. She did not walk until she was 26 months old. She has no peripheral vestibular function. She also has autism.

I say this because I want the Committee to realize or know that CMV has really

changed the way her life was going to look and for our family as well. She's in a lot of ways like any other two-year-old and loves juice boxes and cocoa melon. But our family's trajectory has really changed because of this virus.

And I just want to express why it's so important to screen for CMV. If she had been caught early, she would have been eligible for antiviral treatment, which has been shown to improve long-term neurodevelopmental and hearing outcomes.

I'm just going to reference a few stats. Thirty thousand children are born with congenital CMV each year in the US. This represents about 1 in 200 babies. It's the number-one cause of nongenetic hearing loss, and more children have disabilities due to congenital CMV than Down's syndrome, fetal alcohol syndrome, spina bifida, and pediatric HIV/AIDS combined.

And it's also more common than all of the conditions we currently screen for in the newborn screening panel state by state.

Most babies with CMV show no signs at birth. In fact, physicians are really not very good at identifying babies with congenital CMV just based on clinical suspicion alone. Approximately less than 5 percent are identified by physicians just based on clinical suspicion.

For the most part, these babies look perfect when they're born. But that's because many of the signs lay beneath the surface and cannot be seen, such as intracranial or laboratory abnormalities. And if they do have physical signs, they are sometimes brushed off as being individual variants, just like they were with Evie.

So, why screening for CMV? For several reasons. First, most infants have clinically and apparent infections that were missed in these babies. Second, it must be collected using specimens that are collected at less than 21 days of life. Third, antiviral treatment should be initiated in the first month of life. And fourth, all children with CMV are at

risk of progressive or late-onset hearing loss and require frequently monitoring.

Thank you for your time.

NED CALONGE: Thank you, Samantha.

I'd next like to welcome Taylor Gerding.

TAYLOR GERDING: Hi. Can everybody hear me?

NED CALONGE: Yes. Thank you.

TAYLOR GERDING: Hi. I'm Taylor Gerding. I am the mother of Ava. Ava was born with CMV, or as you guys know, the cytomegalovirus.

My pregnancy was typical, no complications. At 36 weeks I did go in, and I had high blood pressure. That was the first complication I had. They decided to induce me there, and I delivered at 37 weeks.

No complications during delivery. We were in recovery and I was filling out paperwork to be discharged. Everything was fine. A pediatrician came in and expressed some concerns.

Ava couldn't maintain her blood sugar levels. And so that was a concern. And she failed her newborn hearing screen.

But it's funny because they just kind of blew it off and said, "Oh, this happens. No big deal. Don't worry about it."

After that, a neonatologist actually came in and spoke with us. He started asking me more questions, and he asked, "What do you do?" I was very proud of my career, so I answered that I'm a pediatric speech language pathologist. I'm trained in feeding and swallowing.

At this point I will never forget his face. It's still very vivid in my memory. He looked at me with skill, and he said, "Wait. You work with children?" And I said yes. He began at that point to explain to me and my husband that, due to her blood sugars, my job description, and how she at this point had failed her second newborn hearing screen, he wanted to test her for CMV.

We'd never heard of CMV. It's crazy

how three letters can change your whole life. Ava is now two years old. She is thriving at life. She has mild hearing loss. She does have vision loss. She has cerebral palsy, microcephaly, and she's overall developmentally delayed.

That's just to name a few, to be honest. She has so many diagnoses. And every time we go to a doctor, we get a new one. So, I don't even keep track of them anymore. But don't let that fool you. She is one strong girl, and she is very determined.

I feel so blessed to be her mom. She has taught me more about life than I can ever imagine. But because of her CMV, it has caused a lot of changes in our life. I've met amazing families. And after sharing stories, it just always shocks me that we share these stories. And when I tell them that Ava was diagnosed at birth, I'm actually the rare case. A lot of children are not.

A recent study in 2017 said that less than 10 percent of symptomatic congenital CMV

cases are identified. And because Ava was identified at birth, she actually received the antiviral. She was on one called valacyclovir. And she got the chance to slow down or even kind of stop the progression of CMV within her body.

I do think this is why she only has mild hearing loss and mild vision. We've been to multiple EMTs, audiologists, ophthalmologists, and they're surprised that she's not deaf or blind. I can't imagine some of the pain these families have endured because their child wasn't screened or that they didn't have the neonatologist there to kind of ask more questions or really just know the symptoms.

No family -- I don't think any family should have to endure kind of what we have or be impacted by CMV. So, I'm asking you today to please consider and add CMV screening onto the recommended uniform screening for newborns. I think that it can definitely make a difference. As you can see the two different stories you had today.

We can do better for these families so that they can have a chance to get the antiviral, because it has to administered to make an effect within 30 days of birth. That's huge. A lot of times you don't even follow up with your pediatrician until a week old.

So, I just want to thank you for taking the time to listen to me. And just because I believe a picture says 1,000 words, this is Ava. So, this is what congenital CMV looks like. She is happy, but she shouldn't have to go through what she is.

So, thank you, guys.

NED CALONGE: Next I would -- I'm sorry. Thank you, Ava (sic).

Next I would like to welcome Christena Estby.

CHRISTENA ESTBY: Good morning. Everybody can hear me?

NED CALONGE: Yes, thank you.

CHRISTENA ESTBY: Okay. Thank you.

Good morning and thank you for the

opportunity to speak today. My name is Christena Estby, and I have two sons with Duchenne muscular dystrophy. Our family and others hope for effective treatments to slow the trajectory of this devastating disease. We've fundraised and advocated to bring these things to pass during our sons' lifetime.

Samuel and Josiah are adopted. I don't usually introduce them that way; they're simply our sons. However, it is important to notice how they came to us so I can explain why we were able to have the blessing of an early Duchenne diagnosis.

My husband Cory and I had a difficult road to get to the point of bringing our boys home. There's way too much detail for this setting, but we waited an incredibly long period of time to adopt.

I received a phone call from a friend about a seven-week-old baby in need of a home. He had been diagnosed with Duchenne. Samuel's birth mother had an uncle, a brother, and another son

with Duchenne. Because of that, genetic testing had been completed at birth.

We did adopt him, and 21 months later we also adopted his baby brother, Josiah. After bringing Josiah home, we also had him tested at six weeks old. The results confirmed he also has Duchenne.

Our family strongly believes this early diagnosis has allowed for numerous opportunities and advantages that would not otherwise be possible. Samuel, who is now nine, took part in an early steroid use trial. He began a high-dose weekend regiment at 12 months old.

Josiah now is seven years old, was offered the same regiment, which he began at six months old, years earlier than steroid dosing usually begins.

We were able to arrange for specialized medical care immediately. Samuel had his first baseline echocardiogram at six months old, and we've since continued with follow-up appointments every six months at Lurie Children's

Hospital in Chicago. This has allowed even the slightest of changes to be noticed and addressed as appropriate.

Both boys started wearing night-time AFOs at around two years old, which is at least a couple of years earlier than the typical timeframe. Wearing these braces has been documented to help in preventing contractures, which leads to longer ambulation.

They also began physical therapy at around two-and-a-half years of age, a time when many other boys with Duchenne have not even been diagnosed. They work on balance, stability, flexibility. And our physical therapist has implemented a regular stretching and massage routine with them.

The diagnosis process for us took weeks, not months or years, as I've heard of other families sometimes waiting to come a very long time to an accurate diagnosis. We've been told by clinicians that the boys are doing really well.

We've seen videos on social media of

other boys and believe, based simply on a visual comparison, that our sons have less loss of skill and less deterioration of ambulation than their near-their-same-age Duchenne peers.

Samuel does show some hip weakness. He can't always keep up with friends on the playground. He gets tired among outings, but he's doing very well, and makes accommodations, and takes rest as needed.

Josiah is an active little guy with energy for days. He runs and plays and climbs with relative ease. And I truly believe if he didn't know of his Duchenne diagnosis, you might not be able to tell that there was anything to be suspected.

In addition to the above benefits that our family has found, there are so many promising therapies becoming available. Some are only appropriate for a subset of the population. But many will be an option for any number of these boys.

As more and more treatments become

reality, it will become increasingly important to know of a diagnosis as early as possible. Early dosing for many of these therapies could halt Duchenne's progression before it even starts. Early diagnosis could allow for the potential for these boys to live a long and healthy life, a normal life. And that would be a dream come true for all of us.

I'll show you a quick picture. Samuel and Josiah.

And thank you so much for your time.

NED CALONGE: Thank you, Christena.

Next I'd like to welcome Niki Armstrong to provide comments to the Committee.

NIKI ARMSTRONG: Good morning. On behalf of Parent Project Muscular Dystrophy and the Duchenne patient community, and in collaboration with the Muscular Dystrophy Association, thank you for the opportunity to speak today.

You said my name is Niki Armstrong, and I am the Newborn Screening Program Manager for

PPMD.

Listening here from parents like Christena, as well as expert researchers today about the need and importance of newborn screening for Duchenne. But I want to review some key basics in advance of the nomination and prioritization presentation and vote that will occur this afternoon.

Duchenne is the most common pediatric muscular dystrophy with an incidence of around 1 in 5,000 males. It is more common than the majority of genetic conditions currently on state newborn screening panels.

Duchenne is a degenerative condition that worsens over time. The effects of the disease are present at birth, but they are not easily identifiable to a pediatrician or even a Duchenne specialist.

At birth, babies with Duchenne have muscle damage. Over time, that muscle damage accumulates, and eventually the accumulation leads to muscle cells becoming so damaged they die and

are replaced by fat and fibrosa. Once this happens, there is no known way to reverse the damage.

As muscle cells die, people with Duchenne lose skills. They lose the ability to run, to climb stairs, to get off the floor, to walk, to feed themselves -- essentially all activities of daily living. Duchenne is life-limiting with an average age of death in the late 20s.

Treatments for Duchenne, including cortical steroids and exon skipping therapies, slow the progression of disease. When started at the average age of diagnosis, which is currently around age five, they enable walking, upper limb function, and independence for multiple years longer. They slow the decline of heart and lung function and result in a longer lifespan.

Given the mechanism of disease, treatments will be most beneficial before there is significant irreversible muscle damage and when there is more remaining muscle tissue to act upon,

which will potentially provide years of improved function.

Pilots throughout the USA and in multiple other countries have demonstrated the efficacy of CK-MM newborn screening followed by DMD genetic testing. Each pilot has had a slightly different algorithm with different cutoffs. The best that the research goals and planners of that pilot.

Similarly, newborn screening for Duchenne will likely follow cystic fibrosis, with each state individualizing the algorithm to best suit its resources and current mechanisms.

Duchenne currently has five FDA-approved therapies and two additional potential therapies, including gene therapy, under FDA review. Response on gene therapy is expected in just a few short months, at the end of May. For the best outcome, we must identify and treat babies before they have significant irreversible muscle damage.

Newborn screening will provide

optimal opportunities for care and treatment in Duchenne. We ask that you move Duchenne forward to evidence review.

Thank you.

NED CALONGE: Thank you, Niki.

Next I would like to welcome Cara Gagliano to give comments to the Committee.

CARA GAGLIANO: Good morning. Can everyone hear me?

NED CALONGE: Yes, we can hear you. Thank you.

CARA GAGLIANO: Okay, great. Thank you.

So, good morning, everyone. My name is Cara Gagliano. And I'm a mother of three sons, ages -- Jason is 15, Carmine is 13, and Vincent is 10. We live in Brooklyn, New York. And my two younger sons, ages 13 and 10, both have Duchenne.

And I noticed when my son Carmine was about four years old, he was a much slower runner than his peers. He had very large calves, and he had much trouble climbing stairs. I kept telling

our pediatrician that I thought something was wrong. But he kept insisting that my son was just a late bloomer and had full calves.

I was really concerned. And then a stranger commented on the size of my son Carmine's calves. And it just didn't make sense to me. So, I started to research and Google. And all the symptoms that I put in, everything kept coming back as Duchenne muscular dystrophy.

So, I continued to research, and then I continued to convince the pediatrician to do a blood test that I read about that checks your creatine levels, which basically, if it comes back elevated, it's an indication that your muscles are degenerating.

So, I basically had to diagnose my own son, and it took more than three years of us being concerned and pushing and researching before a diagnosis was made. So, he was diagnosed.

We started to see symptoms when he was about four, but he was diagnosed at seven-and-a-half years old, which is considered pretty late.

Most boys with Duchenne are diagnosed around four years old. And then, sadly, after Carmine's diagnosis, it became clear to me that Vincent had the same thing.

So, by the time Carmine started treatment, you know, his muscles were already damaged. Vincent, on the other hand, he started treatment immediately with the standard of care's prednisone steroid treatment and physical therapy.

And you could see a big difference between the two boys. I mean, Vincent starting early, you know, there were a lot of benefits. And I can still see that he keeps up with his peers much, much better than Carmine ever could at 10 years old. He still rides his bike.

A lot of things that Vincent does that Carmine was unable to do at his age. So, I definitely think that early treatment makes a world of difference in this disease.

So, it was a long and grueling journey for my family, trying to convince doctors that something was wrong. And no other parents

should have to go through such an agonizing experience. So, if we have special testing before any symptoms arise, treatment can begin sooner rather than later. And I think that the earlier the disease is treated for the Duchenne boys it will be a better outcome for their health.

So, I truly hope that this screening will be approved, as it can make a huge impact in the lives of boys with Duchenne and their families.

So, thanks for your time today.

NED CALONGE: Thank you, Cara.

Next, I'd like to welcome Megan Waldrop.

MEGAN WALDROP: Good morning. My name is Megan Waldrop, and I am a child neurologist with additional training in neuromuscular medicine and gene therapy. I am an attending physician and Co-Director of the Neuromuscular MDA and SMA Clinics at Nationwide Children's Hospital in Ohio.

Our multidisciplinary MDA clinic is

one of the largest. We follow 506 individuals with Duchenne muscular dystrophy or Becker's muscular dystrophy. And as a group, our team has been pioneers in the care of Duchenne muscular dystrophy.

My colleagues conducted the initial prednisone, daily prednisone studies, and the newer studies highlighting the efficacy and improved safety profile of twice-weekly prednisone, even when initiated in infancy.

In 2016, the first exon skipping drug was approved. And currently there are four exon skipping drugs approved for DMD. And these are safe and efficacious in infants. These drugs are designed to skip a single exon to bring the transcript back in frame to allow these boys to make some of the dystrophin protein that they need.

However, advances continue, and currently gene replacement-like therapies are in development. These are either aimed to replace the missing dystrophin with a shorter, but still

functional version. These are the micro-dystrophin products.

Or there's another design that's using a viral vector to deliver small nuclear RNAs to skip an exon. And this is the vectorized exon-skipping product that's been developed for boys with duplications of exon 2.

I've had the honor to lead the vectorized exon skipping trial. And we dosed the youngest participant ever in a gene therapy for muscular dystrophy. He was dosed at seven months of age, and he has done remarkably well. He's had the least adverse effects of any child in the trial, and he's had continued normal development and had a dramatic, robust, efficacious response.

His creatine kinase levels dropped 91 percent from his baseline, and his dystrophin expression, as measured via muscle biopsy, is over 90 percent in his muscles post-dosing. Pre-dosing levels were absent.

This study has clearly shown in age-dependent dosing effects. We also dosed older

kiddos around nine and thirteen years of age, and they had a significant reduction in protein expression, and also functional improvement, with the oldest child not seeing any functional improvement.

So, we've now shown with multiple treatments that treatment of DMD in infancy is not only safe, but more efficacious, supporting the need for a newborn screening to allow for earlier diagnosis.

Additionally, we've talked a lot about motor function today. But also, there is significant neurocognitive effects that affects these boys. And if we can diagnose them earlier, we can start early intervention to allow them to have the fullest potential for functioning in society.

Thank you for your time.

NED CALONGE: Thank you, Megan.

Next, Paul Melmeyer.

PAUL MELMEYER: All right. Thank you very much. Thank you for the opportunity to

comment on today's deliberation on moving Duchenne muscular dystrophy forward to full evidence review.

I am Paul Melmeyer, Vice President of Policy and Advocacy at the Muscular Dystrophy Association. MDA is proud to serve the Duchenne, spinal muscular atrophy, and Pompe communities, along with many other rare neuromuscular diseases.

Today we request the Committee to vote to move the Duchenne muscular dystrophy nomination forward to full evidence review. MDA was proud to co-sponsor the nomination of Duchenne last summer, and under the leadership of Parent Project Muscular Dystrophy provide the evidence the Committee required for consideration.

I'd like to emphasize several points as the Committee considers its vote. First, we believe the evidence within, or reference within the nomination package is thorough and adequate to move the nomination forward. Duchenne is certainly a serious disease that would benefit from early diagnosis and early treatment.

Progression of Duchenne is well understood due to decades of research funded by MDA, PPMD, and other allied Duchenne organizations.

Second, MDA was pleased to co-fund the pilot study conducted in North Carolina by RTI International that tested the validity and reliability of using creatine kinase levels in follow-up confirmatory genetic testing to screen for and diagnose Duchenne. This pilot study, along with studies in New York and Massachusetts, has shown the feasibility of screening for Duchenne first.

Third, there are several FDA-approved treatments available to individuals with Duchenne, including several exon skipping therapies, as well as corticosteroid treatments. We also anticipate a gene therapy to be approved by the FDA later this year for Duchenne.

Like treatments in similar neuromuscular diseases, treating Duchenne early can help slow the progression of irreversible

muscle loss and organ damage.

Finally, a robust network of clinicians are prepared to offer comprehensive care to those who are newly diagnosed. Often, these are the very same clinics treating infants newly diagnosed with SMA and Pompe, thus creating a familiarity within the neuromuscular disease clinical community for care and support of those diagnosed through newborn screening.

These clinics are also usually familiar with any related neuromuscular disorder that might be caught through the screening.

In conclusion, we urge the Committee to vote to move Duchenne muscular dystrophy forward to full evidence review.

Thank you.

NED CALONGE: Thank you, Paul.

And finally for public comment today we have Dylan Simon.

DYLAN SIMON: Good morning. And thank you for the opportunity to speak with you today.

Again, my name is Dylan Simon, and I serve as Director of Policy for the EveryLife Foundation for Rare Diseases. The EveryLife Foundation is a nonprofit, nonpartisan organization dedicated to empowering the rare disease patient community to have impactful science and legislation and policy that advances the equitable development of and access to lifesaving diagnoses, treatments, and cures.

EveryLife and our rare disease community partners are grateful to the Committee's many efforts to conduct thorough and thoughtful evidence reviews of nominated conditions.

We further understand, as described in the statute, Section B, under the Duties section that the Advisory Committee shall, quote, "make systemic evidence-based and peer-reviewed recommendations that include the heritable disorders that have potential to significantly impact public health for which all newborns should be screened, including secondary conditions that might be identified as a result of laboratory

methods used for screening," closed quote.

Yesterday's discussion and vote yielded a seven-seven vote. That tie vote was interpreted at the conclusion of the Committee meeting as a vote of not to move Krabbe to be forwarded for consideration by the Secretary. The rare disease community urges this Committee to reconsider the interpretation of the tied vote.

Indeed, yesterday did not yield a no. Instead, it yielded a need for further clarification of questions that were raised and discussions that could not be addressed by participating members of the discussion.

Furthermore, in the same Advisory Committee charter, with section C of the membership items states that, "The general shall appoint not to exceed 15 members of the Advisory Committee. In appointing such members, the Secretary shall ensure that the total number of membership of the Advisory Committee is an odd number."

While the charter does not

specifically require the purpose of the composition of the membership being an odd number to ensure that no vote ever ended in a tie, we believe strongly in providing a path forward for further discussion and resolution of this tie that in keeping with the intention with which this Advisory Committee was established.

For this reason, the EveryLife Foundation and the rare disease community urge the Advisory Committee to revisit the conclusion of yesterday's vote and consider options for ways to ensure that the Krabbe disease nomination receives a full and complete consideration that it's deserving.

Further, we appreciate the efforts to date to enhance the evidentiary nature. But yesterday's discussion illuminated critical gaps in the data, being as they are essential and committed to decision-making.

Our current decision-making model that informs the benefit/risk tradeoffs are not yet comprehensively inclusive of critical data and

elements and considerations that reflect patient experience data. Data which is defined in statute and is not required as part of the decision making may bring ecosystems such as our regulatory partners at the US Food and Drug Administration.

In your ongoing assessment to ensure that the decision of this Committee in fact is in the best interests of the public's health, we urge the Committee to expand and formalize the data included in the evidentiary matrix.

In addition, related to the composition of the members of the Advisory Committee to participate in discussion during review of a nominated condition, the presentation of evidence review, we have the following recommendations for the Committee:

We once again request the Committee add a patient representative as a voting community member. As defined by the National Health Council and adopted by FDA reviews and the PFDD guidance, collecting comprehensive representative input, quote, "representativeness means a sufficient

number of and types of people are included in engaging activities to ensure that those engaged can speak on behalf of the target population. Discussions that articulate and project experiences and opinions of said community that lacks formal representation reflects significant imbalance in representation."

Second. During every discussion or interview, we ask the Committee to formally include an expert member of the nominated disease community to participate in the discussion, to be available to address questions that arise and inform the discussion.

As an example, yesterday's Committee discussion included significant time devoted concerning about the impacts screening might have on families identified as false positives based on older literature that actually has since been updated.

In addition, yesterday's discussion also included discussion of late-onset phenotypes of a condition where the nomination was specific

to infantile onset Krabbe.

Yesterday's discussion contained a third discussion about the perceived negative impact for receiving late-onset diagnosis for families. However, recent data from the BabySeq experiment showed that at three months on in the participation, 86.8 percent of parents were very interested in receiving information on their babies' risk of developing disease in childhood that could be prevented, treated, or cured.

In addition, 84.6 percent were interested in receiving information regarding if their baby was at risk for developing a disease in adulthood that could be prevented, treated, or cured.

During the conduction of their interviews, discussions, we urge the organizational representative be permitted to participate in discussion.

Had they been invited onto the Committee because of the fact they represent stakeholder groups who are vital to the newborn

screening ecosystem, silencing their perspectives at a time that ardently matters the most negates the purpose of their membership.

Thank you for the opportunity to speak in front of the Committee today.

And we're dedicated to rare diseases in the community. EveryLife Foundation and members of the Community Congress and newborn screening and diagnostic working group look forward to the continuing engagement with this Committee in the coming months.

Thank you so much.

NED CALONGE: Thank you, Dylan.

I do want to make a comment regarding the discussion. I realized after the session that I implied that we wouldn't take comments from the organizational reps unless they were asked by Committee members.

I apologize for that incorrect implication. And I do want to reiterate that during the discussion, my intent was to say we wanted to hear from Committee members who vote

first. And then if time allowed, turn to our organizational representatives.

I realize that is not what I presented, and I apologize to our org reps. I will say that we did run out of time in taking questions and comments from the Committee members. And I assure -- and that has happened in past discussions and votes as well.

So, I apologize especially to our organizational reps for that misstatement. And we'll assure you that I understand the way that your expertise that you bring to the table and why you're here. And if time allows during the discussion, as we've created the agenda, I will ensure that we allow those comments and questions to come forward.

Thank you. I would like to move on to the next session.

WORKGROUP UPDATE: EDUCATION AND TRAINING WORKGROUP

NED CALONGE: That is the report out from the workgroups. And I would like to start

with the first group's report coming from the Education and Training Workgroup and Jane DeLuca.

Jane is an Associate Professor at the School of Nursing at Clemson University in South Carolina since 2012. She has a clinical appointment at the Greenwood Genetic Center in the Metabolic Clinic, caring for newborn screening patients and others within more areas of metabolism.

I'd like to turn things over to you, Jane.

(Pause)

NED CALONGE: We're not hearing you yet.

(Pause)

JANE DeLUCA: Okay. Can you hear me now?

NED CALONGE: We can.

JANE DeLUCA: Okay. All right. Here I was sort of just talking along.

JANE DeLUCA: So, I just want to thank the Committee for meeting yesterday, and

thank you, Ned. We had a robust discussion.

Next slide, please.

(Slide)

JANE DeLUCA: I just wanted to fix on this for just a minute so you could see all of the members of the Education and Training Workgroup.

Next slide, please.

(Slide)

JANE DeLUCA: So, the first thing we discussed was the proposed changes in the existing structure of the workgroup. So, it was suggested that the formal workgroups dissolve in favor of smaller workgroups that are focused on specific prioritized projects.

So, in terms of our discussion, in some ways Education and Training has always operated in this manner and has broken out into smaller workgroups, and they've actually been quite productive. So, we just want to make that clear.

And also, we've spent some time talking about the potential downside of having

smaller workgroups, that you could spend excess time identifying and recruiting people for these specific workgroups, and that could take energy.

The Education and Training Workgroup we feel in the past couple of years has been underutilized. And we also wanted to think about, what is the impact of this Committee? Because there have been projects that we've completed in the past. So, what is the impact of what we've actually done?

So, we're actually trying to get back a little bit to the Advisory Committee. We have ideas, but does the Advisory Committee have specific things that they want us to work on? And guidance from the point that was made in this discussion is that understanding what resources we have available to us may actually --

Next slide, please.

(Slide)

JANE DeLUCA: So, I just wanted to go back to --

NED CALONGE: Jane, I'm not hearing

you now.

JANE DeLUCA: -- previous meetings. We were charged with -- okay. How about how?

NED CALONGE: Yes.

JANE DeLUCA: Okay, I'm back. Back in the saddle.

So, I just wanted to go back to our previous meetings just to reiterate some of the work that we've done. We were charged with identifying three top priority solutions that the Committee can consider to act on to support state implementation of conditions added to the RUSP.

So, from several ideas, we actually ended up with a kind of a broad statement in terms of partnering with governmental agencies, professional groups working in similar spaces. And we'll support development, distribution, and awareness of diverse and culturally focused new and existing newborn screening education programs and materials, and ensuring coverage of basic genetics and newborn screening for all.

This is a very sort of broad take on

this. And if we're going to be having more small, discrete projects, this actually may be a little bit too broad.

So, next slide, please.

Can you hear me? Next slide.

(Slide)

JANE DeLUCA: Okay. So, -- yes?

NED CALONGE: We can hear you.

JANE DeLUCA: Okay.

So, we went back to two previous projects in terms of the educational planning and communication guide. And these are located on the Advisory Committee webspace. So, these were projects that the group undertook. And they had a lot of work that went into them, and they're actually very comprehensive and very valuable.

NED CALONGE: And now we're not hearing you.

JANE DeLUCA: So, one of the things that we -- I apologize.

(Pause)

NED CALONGE: Jane, you might try

turning your camera off.

JANE DeLUCA: Yeah. I'm going to do that. How's that? Does that work?

NED CALONGE: It seems to be working.

JANE DeLUCA: Okay. I'm getting an "unstable" message. So, I apologize for this technical problem. You can still hear me?

NED CALONGE: Yes.

JANE DeLUCA: Okay.

So, we went back to two previous projects. It was development of the educational planning and communication guides. And a lot of work went into these. And we viewed these as very valuable. But one of the things we were thinking about was, how can we know whether people accessing these, you know, is there a mechanism that we can tap for that?

Next slide, please.

(Slide)

JANE DeLUCA: So, the past. How do we evaluate completed work? So, what is the impact of screening guides or other resources?

So, how can we evaluate their use? So, in terms of who's using them, how often, and what approaches and metrics can we use, we were thinking of trying to devise ways of either looking for IP addresses or other means for understanding how people are accessing these materials.

And in terms of this, so what does successive education in newborn screening look like? What changes are we seeing? So, we feel like there needs to be this evaluative process in terms of materials that we've produced but maybe that other agencies produced as well.

Next slide.

(Slide)

JANE DeLUCA: In terms of the present, for study priorities, one of the things we came up with is fostering community engagement, which of course programs aren't doing now. How do we use our volunteer energy for projects prioritized by communities that are steered by the communities themselves?

We can engage states' newborn screening programs to understand the needs of different groups, particularly groups that are perhaps underserved or challenging to reach. And we can check in with state programs for their policies and materials that they have developed for newborn screening.

Maybe we're able to access existing organizations and identify grantees for assistance in performing needs assessments for looking at, for example, state policies or state education programs.

And also, we talked about understanding the parents' and families' experiences in newborn screening, pairing families of infants who have gone through screening with positive or false positive results.

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(Slide)

JANE DeLUCA: Yeah. Okay. So, further priorities for the present. Can we create a repository for our vast newborn screening

resources? Well, don't reinvent the wheel. And perhaps there's no value to the piece we can put there in terms of looking at these materials.

Written materials, pamphlets cannot get the message out about newborn screening. Other means may do a better job. HRSA Baby's First Test has YouTube videos and channels on these existing materials in different states such as California and Texas that also are using YouTube.

But creating YouTube education for newborn screening or PSAs can be very expensive. And we may have to tap different types of marketing groups and so forth.

Again, another priority that we could have is thinking about newborn screening education while on the continuum of the process from obstetrics to pediatric. First pediatric --

(Pause)

NED CALONGE: Jane, I'm so sorry.

Now we can hear you again. You're good. Nope, you're not.

(Pause)

JANE DeLUCA: How about now?

NED CALONGE: Yes. Back to you again. Thank you.

JANE DeLUCA: Okay. All right.

So, thinking of newborn education on a continuum. And what's doable for a newborn screening education, but again with this measurable piece.

Next slide.

(Slide)

JANE DeLUCA: And then the future. What do we look for and how do we prepare? We need to provide education for communities and parents about new disorders that will be added to the RUSP and also provide guidance and education for understanding genomic sequencing for newborn screening which is on the horizon. There are already companies engaged in this and multiple research projects for that.

Last slide, please.

(Slide)

JANE DeLUCA: So, where to from here? A useful framework. We can look at the past, the present, and the future. And the Advisory Committee vision and ideas for project-oriented workgroups with education and training can help set priorities and acquire funding. We have many good suggestions on what to do, but we need ongoing conversations to prioritize these ideas and set potential projects and form the task groups.

That's the end of the presentation.

Thank you.

NED CALONGE: Thank you, Jane.

So, we're going to go through all of the presentations, and then turn to the Committee and the organizational reps for questions and comments.

WORKGROUP UPDATE: FOLLOW-UP AND TREATMENT WORKGROUP

NED CALONGE: So, now I see here from the Follow-up and Treatment Workgroup. And Kyle

Brothers is an Associate Professor of Pediatrics and the Endowed Chair for Pediatric Clinical and Translational Research at the University of Louisville.

Dr. Brothers' research focuses on policy and ethics in human genetics and the translation of health technologies in the clinical care. Dr. Brothers is a practicing primary care pediatrician and serves as the Chair of the Ethics Committee at Norton Children's Hospital in Louisville, Kentucky.

Kyle.

KYLE BROTHERS: Thank you so much.

Once again, we had a great discussion at Follow-up and Treatment Workgroup.

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KYLE BROTHERS: As a reminder, in November 2022, our last meeting, the group reached consensus on basically requesting a blueprint for follow-up and treatment as part of RUSP nominations. And the goal of this blueprint was

basically to serve as a starting point for guidance materials for states after the addition of a condition to the RUSP.

And incidentally, as we can discuss a little bit, I think some of these elements that we're proposing of such a blueprint might actually help with the review itself and sort of pinning down certain items that are sometimes hard to get out of the proposal.

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KYLE BROTHERS: So, yesterday we focused on trying to take that more general idea and come up with next steps. So, our proposal to HRSA is basically to help start the process by drafting a revision to the RUSP nomination form that would include three elements of a blueprint. And over the next three slides, we'll look at the three proposed elements.

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KYLE BROTHERS: So, first we are

breaking down the mission of the Follow-up and Treatment Workgroup into basically three steps: the short-term follow-up that basically is sort of in the domain of the newborn screening programs to assess the screening program; two, long-term follow-up which is more in the health care system domain; and then third, the treatment.

So, the first item we suggest be included in this blueprint would be for the nominators to suggest a short-term follow-up plan for the state newborn screening programs to assess their program.

So, what happens when a baby screens positive? Like what are the next steps? And just as an example, responses to this kind of item might include an algorithm that shows for different levels of biomarkers, et cetera. What happens? What's the next step?

Then what short-term outcomes should the states specific to this condition need to gather to evaluate the short-term or the screening outcomes? So, that's item one of our proposed

blueprint to be added to the RUSP nomination form.

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KYLE BROTHERS: And the second one is long-term follow-up and treatment approach for minors. So, basically, specifying where are the relevant subgroups, maybe providing suggested standardized terminology.

This would help get everyone on the same page about, what are the different subgroups of screened individuals and what's their long-term follow-up? Basically, how would each group be managed? So, you know, testing, follow-up, treatment for some groups.

And then for conditions that actually have existing clinical practice guidelines, a response to this kind of item might be very straightforward because the nominators might just need to reference the clinical practice guidelines.

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KYLE BROTHERS: And then finally, we believe it is really important for every condition that gets added to the RUSP to basically have a data collection strategy in order to assess that. Several people brought up the last time a condition went to the Secretary. It was added to the RUSP. With it, the specification that our Committee needed to provide an update in five years on what's happened.

So, we think this is going to be a request that's going to recur. And it's therefore important to have a data collection strategy from the beginning.

And just some suggested items that might be elicited in the nomination form, one would be a suggested data repository location or platform. As you all know, there are several places that are collecting this kind of information that could be used. Some are disease-specific, some are not.

But it would be good for the nominators, who often include folks who are very

knowledgeable about the condition and the research, you know, environment for that condition. Where should data about the implementation of newborn screening go?

And then second, it would be great to get some specifics about the variables that would be needed to evaluate the addition of the condition to the RUSP, including both the screening outcomes and the treatment outcomes. And I think it's -- you know, it's apparent individual conditions have different dynamics. There's different subgroups of screening folks, folks who are classified as having a condition, those who are classified as being at risk for a condition, et cetera.

So, really, specifying these variables and what the categories are would be critical and help create a more consistent plan for gathering data across states.

Next slide, I think it's my last

(Slide)

KYLE BROTHERS: Yes. Okay.

Thank you so much, Dr. Calonge.

NED CALONGE: Thanks, Kyle.

WORKGROUP UPDATE: LABORATORY STANDARDS AND PROCEDURES WORKGROUP

NED CALONGE: Our next presentation is from the Laboratory Standards and Procedures Workgroup.

And Kellie B. Kelm is going to present. Kellie has worked at the US Food and Drug Administration for almost 15 years, including more than 8 years as lead reviewer of premarket submissions, investigational device exemption applications, and pre-submissions for chemistry, toxicology, genetic, genomic, and newborn screening devices.

Dr. Kelm is the FDA representative to the Advisory Committee, and I look forward to your presentation. Thanks, Kellie.

KELLIE KELM: Thank you.

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(Slide)

KELLIE KELM: We had another great

processes that they participate in.

They would like to match Florida Vital Stats data with newborn screening data within the lab information management system. They'd like to explore the need for health information exchanges within newborn screening. They'd like to explore the use of FHIR within newborn screening electronic orders and results and explore how newborn screening processes could be improved by the use of HL7 messaging.

And so, while we knew that those were some of the recommendations and some of the leading standards, it was good to hear that from these stakeholders, the trading partners, and the staff who aren't necessarily involved in the technical process for newborn screening.

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(Slide)

JUAN VASQUEZ: So, again, as we planned, we had to identify who the key stakeholders were. And in understanding who the key stakeholders were, we wanted to look at one,

and I just want you to know how much I appreciate you all being here and being present and really taking on the task with so much sincerity, respect, and earnestness. So, thanks a lot.

The next meeting will be hopefully in person, May 4th and 5th. I'll let you know if there are any changes to our plans to have the meeting in person. And we will be contacting you with things like prioritized lists for work, for topic groups, as discussed by the workgroups. We'll be doing that in the interim, plus other business as it comes up in front of the Committee.

If there are no other comments, questions, I will declare the February meeting adjourned. And I'll be talking with you all soon.

(WHEREUPON, THE MEETING WAS CONCLUDED AT 2:00 P.M.)