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

- I N D E X -

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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.

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(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.

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(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.

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(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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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.

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(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.

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(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.

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(Slide)

ALEX KEMPER: In terms of key points --

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(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.

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(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.

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(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.

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(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.

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(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.

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(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 --

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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?

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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.

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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.

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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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KELLIE KELM: We had another great

discussion yesterday, and I want to thank -- most of the members were able to make it virtually. So, Susan, my co-chair, and I, we had a great discussion with the group on the three topics that we have.

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KELLIE KELM: And the next slide after that.

(Slide)

KELLIE KELM: So, what we did was spend time discussing the three -- these are the three topics. The solutions that we had talked about at the last meeting that the Committee had endorsed that we continue to work on. So, there are a few things that we did.

We obviously talked a little bit more in-depth on the proposals and where the work had started. And we were talking a little bit about, you know, if these task groups move forward, some names, some folks that were really interested and shared a lot of their experiences.

And let me remind you a little bit about each of them as we go through. And we actually proposed to change the rank of priority of the first two. I can talk a little bit about that. Some of that was even about yesterday's Committee discussion.

So, the one topic is drafting a best practices document for states to use when considering the utilization or addition of second-tier testing, including utilizing reference and/or regional labs. And we thought that this was even more pertinent after yesterday's discussion, for example, of psychosine testing.

Spent a little bit of time on the experience that we heard yesterday afternoon from members.

And as we even described back in November, you know, I think the idea for this type of document is that it would be used by states that were considering both prospective addition of second-tier testing for new conditions and when they are looking at conditions they already

screened for, but have considered whether the addition of the second-tier test would be something to work on perhaps because of, you know, higher false positive rates than they'd like or even the creation of second-tier tests that they'd like to consider.

So, we talked a little bit about, again, experiences and a little bit more about what states would find more informative for a document like this.

You know, they do think that as part of this document outline that would be used that states would use to consider for any condition sort of a table that would include probably the most relevant scientific and/or technical information that would be gathered for a condition of interest when, you know, going through this thought process.

And I think the biggest lessons learned that we heard from folks was when contracting out, again whether this is a reference or some sort of a regional laboratory, that this

was one of the biggest lists in difficult processes that states went through.

And we realized that obviously some states may have different processes depending on their administration, that it might be possible to make some information -- help states on the path to what to gather and put together that would hopefully make that process a little less painless (sic).

So, we heard from, for example, Patricia Hall is on here. Apparently works for Mayo, and she has worked both on the state public health side as well as, you know, a lab that is used by states. And so, she is really enthusiastic about helping out because she has had both hats on. So.

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KELLIE KELM: And this was that one we had already proposed, a one-year timeline, and we think that's still achievable. The other one that was sort of the top priority was the quick-

start guide and project plan worksheet for implementation of the condition added to the RUSP. And so, this is the one that had the two pieces to it.

You know, there are already some resources in this space. So, we heard in our discussion, you know, that some states have already used and found useful the information that's out there. Often these are APHL-created documents or documents -- or we've heard from other states that they were good starts, but they weren't exactly what they were looking for when they were implementing a new condition for their states.

So, I think for this one, what we heard was that obviously we need to make sure that we're starting by compiling information that states are using and what else that they would like in order to help implement conditions more rapidly.

So, obviously, gathering existing fact sheets, tools, and information that have been

created by other groups, and assessing those for gaps, and thinking about the new quick start guide and product and client worksheet. And then developing a dissemination plan so programs can use them and obtain them.

So, you know, we also obviously heard that some of these things might exist, and some states may not have heard about them. So, how can we do a better job disseminating them and publicizing their availability?

So, again, you know, some of the interesting conversations that we had, especially so starting with the first, the fact sheet, where we know there's already the public health system assessment fact sheet that's created. And then that is often used by states.

As well APHL's NewSTEPs to disorders, new disorders workgroup is to again start with this process of looking at what already exists and thinking, What are the gaps?

And one of the comments was that I do think is important is including some sort of a

process where there is a regular interval where these documents would be revisited in order to, for example, screening technology or other things do change, and to make changes using a rigorous and robust process as appropriate.

And obviously then, having a plan to update the quick-start guide when RUSP is updated as well. So, that's come up before. If that happens, you know, include that in this plan as well.

And in the project plan worksheet, you know, what we heard from some states is that they would also -- and although there is and has been a peer-resource network that if you don't provide in the past with some activities, that people also wanted to discuss whether we could create or add peer-led resources to help implementation, to answer questions that aren't in the current peer lab resource methods.

So, again, we heard from states that something like that would be really helpful to them as they are implementing a new condition.

So, just adding some here, and again this is somewhere where we had some folks who were really interested based on their experience, their role on APHL workgroups, and obviously APHL has a lot of resources already.

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KELLIE KELM: And the last one, we unfortunately didn't get much time to get to the last one. The discussion on the first two took up most of our time. But we did get a little bit of an update. So, if you recall, the concern is that screening for homocystinuria is -- I'm trying to think of the word -- is not as effective as I think states would like it to be.

And wanting to improve the false negative rate, and we've heard about that before from advocacy groups as well as the states. So, we got a little bit of an update.

You know, CDC has been working on this issue. And it was something that we would plan to fold into this evaluation of current

methods and talking about whether or not there might be more appropriate methods. And CDC has been working on this. And at this time, they didn't have many details to share except that they're working on perhaps a first-tier and/or second-tier test to share.

And the thought was that this group would obviously, you know, while that's still being worked on, make sure that as far as evaluation, putting in one place the information that we've heard about on the issues with the current paradigm in use by states. And that obviously, gathering that information from states and advocacy groups and clinical experts as part of the process.

So, that's it. Anyway, great meeting of the workgroup and a great, more robust discussion of these three solutions.

So, thank you.

NED CALONGE: Thanks so much, Kellie. And also, Kyle and Jane as well. The groups did great work yesterday, and it's very exciting.

COMMITTEE DISCUSSION ON ACTION ITEMS

NED CALONGE: I'd like to open things up now to the Committee for discussion. Again, Committee members will discuss first. And we'll take the comments, questions, and suggestions from organizational representatives after that.

Please use the raise hand feature, and please remember to unmute yourself, and state your first and last name each time you ask a question.

So, I will just start by again thanking the Committees. I think each Committee came up with recommendations that I believe the Committee, this Committee, could prioritize. We have three more meetings in 2023. And thinking about what we would like to prioritize to try to achieve with our time together this year and to request support if it's available from HRSA is kind of the way I would like to proceed.

They do not have many -- we want to prioritize, I think, maybe somewhere around two to three things we think we could achieve in a 12-

month period of time, is the way I would think about it. And then of course we'll welcome comments and clarification from our HRSA colleagues as well.

So, I'm going to try to do my best at remembering, I think that Education and Training talked about evaluating what we've done so far. It's doing a better job of disseminating what we've already created and maybe improving those products and thinking about specifically designed training and education materials for newly added conditions to the RUSP.

Or the next group, Kyle's group, I would see that as really a single recommendation with three parts, which is to create a topic to work on the blueprint for treatment and follow-up.

And for the last group that Kellie just presented, we had a prioritized list. And I appreciate that, one being at second-tier testing. And the second, the quick-start guide. And then the third, which I should remember better because that's the one I just heard, but it was the third

rank. I feel better for that.

So, those were the kind of nine issues we had.

And, Kellie, can you just remind me of the last one? I'm sorry.

KELLIE KELM: Yeah. Homocystinuria screening.

NED CALONGE: Homocystinuria. I do. So, specific; that's why. And it had a longer, two-year timeframe.

So, with that kind of preamble, I will entertain questions and comments and suggestions from the Committee.

And we're going to start with Ash.

ASHUTOSH LAL: Thank you. My name is Ash Lal. Just a couple of quick comments.

One thing on the educational materials that are created, I think we have to acknowledge the base of discovery and new therapies being developed.

And also I think just the fact that the condition is being initially screened, the

number of patients and experience gained, and the better understanding of the natural history of the disease and so on, and the Becker interventions -- all of these to me mean that there has to be some periodic review and update to the education materials.

Not that every condition is going to need it, but just to review, at a certain time interval that could be proposed for different conditions so that the materials are keeping pace with what's known in the scientific literature on the condition.

NED CALONGE: Thanks, Ash.

Scott.

SCOTT SHONE: Thank you, Ned.

Scott Shone, org rep, ASTHO.

So, I think that -- you know, my comment would be, across the board it sounds like there is a need for I think what Jane was saying, which is this review and refresh of everything that already exists. Because we heard it in the lab group, and some people even said, "Gosh, I

wish I knew this existed." And these are documents that some of us have known for a while.

But, you know, we've heard over the last couple of years about the workforce shortages and turnover. And there's a lot of new faces and new perspectives in the system who are completely unaware of the immense work that many people either on this Committee on in the org reps have done largely with HRSA funding.

So, I think it would behoove HRSA to really think about what they've funded over the last five to ten years, including an education repository, including a laboratory technical assistance program, including all of the things that all of these three presenters just talked about and not put a lot of effort into rebuilding things, but looking at what's already done, has worked incredibly well for many of us who have worked in the system for over a decade, and remind the new people, as well as the older of us that these exist and can be used.

Because it seems silly to throw money

at creating new resources when there's so many wonderful things that you've already paid for that have been used elsewhere. And perhaps look at opportunities to take some of the resources that are developed for the program agnostic use and help us in space and programs to think about how to tweak them that are more specific for that.

Whether they're implementation guides, whether they're information about how follow-up, short-term, long-term, depending on what you have in your state works. But I would encourage that approach first before taking on new developmental projects. Because we end up having this discussion over and over again. And I think that we are doomed to continue to repeat our history if we have not yet learned from it.

NED CALONGE: Yeah. I appreciate your comments, Scott. And I think, thinking about what Ash said and you just said, I have a project that would review and revise materials that already exist to support newborn screening implementation and education is one activity.

The other thing I kind of heard from Jane and I thought about as you were talking about is, groups like the DHDS and the CPSTF, CDC's community guide, have dedicated resources to dissemination. And to Jane's point, part of the dissemination strategies, they have ways of keeping track of how many people are using the materials?

I mean, these are all commonly available strategies online to help look at the impact of the uptake and use of materials and information available. So, if I was going to restate what you said, Scott, I hope that I'm being accurate, it's, think about what we have. Review those. Think about what needs revision and refinement. And then a dedicated dissemination strategy might be an approach that we could take.

Kamila.

KAMILA MISTRY: Thanks, Ned.

I just want to build on that because I think it's so important to stop and really think about the impact of the work, and then also as

reviewing that, almost think about, where are there gaps? Where aren't we reaching, filling that we need to be doing that as we're kind of thinking about it?

And also, I think learning from it more systematically about, what are those lessons learned that we can think about for the future in terms of investments, in terms of resources? So, maybe a little bit more of an evaluation, needs assessment, kind of more systematic I would say, I think is usually helpful.

NED CALONGE: Yes. Thank you.

Michael.

MICHAEL WARREN: Sure. Thank you. I appreciate those comments.

I think there are a few things to note. One, Dr. Shone, you're pointing out and making sure folks know about our current resources is really important. I think we could work through our TA center current funded TA investments on that, I know.

And some of our other programmatic

areas, like Title 5. We do make a concerted effort when there's like a new state Title 5 director to reach out to make sure there's an orientation, for lack of a better word, an awareness of resources.

And I think the current TA work does that to come extent, with the newborn screening staff. And we think about how we make that more available because, as you said, there has been a lot of turnover. I think the clearinghouse that we're required to do also is a great place to make sure that information is available and we can look at whether places -- that some of that can be updated.

A couple of things, and Dr. Calonge shared two NOFOs that are currently posted. I think those NOFOs are a direct result of what we've heard from this Committee over a number of years. People have got ways that we can better support states in the field. So, excited that those are out and look forward to what is hopefully a robust response there.

And then also just wanted to share some very recent collaboration we've been doing with colleagues at CDC. We actually took a team down to Atlanta last week to look specifically at our newborn screening portfolio, both with their lab folks and their folks in the National Center for Birth Defects and Developmental Disabilities.

To see where we can make sure we are coordinated and aligned, reducing burden on our state awardees, things like, are there ways we can commonly define performance measures and simplified data collection as one concrete example. But also to make sure we're filling in any gaps.

Appreciate your thoughts.

NED CALONGE: Thanks, Michael.

Shawn.

SHAWN McCANDLESS: Thank you. Shawn McCandless, Committee member.

Regarding the issue of dissemination, and I think several people have alluded to this, or maybe not directly. But there's an inherent

bias against rare diseases in our field, in the field of medicine. And most of what we deal with are rare diseases. So, to pediatricians, newborn screening is typically normal. And if it's not normal, it's a false positive.

So, there's -- we create lots of resources. But we just have trouble generating -- we have trouble generating enthusiasm for people to read the things we produce or to make them available or even to care that they're out there.

And, Ned, you mentioned the US Preventive Services Task Force and their dissemination. You know, they get a monthly journal article in JAMA describing their most recent findings. Is JAMA interested in publishing even once a year something about newborn screening? I doubt it.

There's just inherent bias against rare diseases in spite of the fact that rare diseases are incredibly common. It's just across, you know, in our society. You know, the numbers I think are one in ten people live with some sort of

rare condition.

And I don't know how we overcome this bias. So, I don't have an answer. But I think that it's important for us to face the issue that there is a very -- that we have a big communication problem, and that is that people think that everything we talk about is rare, and they don't care.

Until they do care. And I think that that's where part of the answer is, that everything that we do has to be easily discoverable and just-in-time, right? It has to be short, it has to be effective communication, it has to be easy to find by doing a Google search.

Nothing I just said is news to anyone. But I think it's important that we be up-front about it.

(Inaudible interjection)

NED CALONGE: Thank you for these comments. And again, it got me thinking about other experiences. So, a couple of things with the Preventive Services Task Force, its

strategies, I think, would be worth thinking about.

The task force has a relationship with JAMA. And it was changed to JAMA right as I was leaving, as I was turned off the task force. It was with the American Journal of Preventive Medicine before that.

And the agreement was to publish a journal-oriented version of the systematic evidence review. Because we do publish systematic evidence reviews.

Now, someone has to write it, to match the journal, you know, to make it journal-ready. But because that's important to the EPCs, the evidence review groups, they are happy to do that and are thinking about publication when that happens. And the journal agrees to publish the recommendations.

And I wonder if we thought about, thinking about a similar relationship that we could at least pursue or ask about with the Journal of Pediatrics. I mean, that's the one I

would think about. Or I guess we could go to Genetics and Medicine as we move more into molecular diagnosis.

The American College of Obstetricians and Gynecologists, the Green Journal. I think it might be worth -- and, Michael, I don't know how this jives with HRSA. But clearly AHRQ does it, and I think the CPS staff has a relationship with AJPH. And think about dissemination through journal articles.

Now, I recognize, I want to point out that I understand that's half of the target audience, if you will. So, as I was thinking about dissemination, I tend to think about dissemination to providers. And I hope that bias makes sense. Because that's where there's a systematic way of providing new information in terms of continuing medical education and recertification for boards.

So, I think there are ways to address one-half of the dyad needs to be trained and educated and more cognizant of rare diseases and

newborn screening, which would be the providers.

I would turn to my colleagues in the community to think about how to create better awareness among the general public. I mean the issue about the diffusion of information beyond these groups that we have access to is always a little bit more difficult.

And since most people having a baby will somewhere impact the health care system, I think that is not an unreasonable group to think about dissemination strategies. So, I'll stop my diatribe and turn back. I do see some organizational reps' hands. I'm just going to go to Committee members first. And I know you're there.

So, Michele, I wonder if you'd like to comment next.

MICHELE CAGGANA: I was going to hearken back to what Shawn had said. We've had in newborn screening many situations where we've called and we get the response from the parents after diagnosis that, you know, the doctor told

them that it was nothing. And that the message they got was quite different than the reality.

And so, I think working on dissemination of that kind of information, and having it like the ACTsheets just in time is very helpful.

When I would speak to med students, I always used to tell them that it's not rare until it happens to them and their patients, and try and keep that sort of in the forefront of their brain.

The other thing is I'm very happy about the HRSA-CDC collaboration perhaps on aligning the requirements that we need when we get grant funding. And I think that will help the entire newborn screening community as well.

And then last week -- I think in light of a lot of yesterday's discussion, the prioritization of the Follow-up and Treatment Group that Kyle discussed would be something that I think would be quite useful from the perspective of the people who are nominating conditions and then also to help us better be able to assess the

evidence and what we're provided to review.

Thank you.

NED CALONGE: Thanks, Michele. Great comments and suggestions.

Carla.

CARLA CUTHBERT: Yeah. I just wanted to then, on the back of what Michele just said and commenting on what Michael Warren referred to, we were really excited to have a robust group from HRSA come to visit us at CDC and were able to really address some of the things where we do have some overlapping series of activities, to make sure that we are being strategic about how we're supporting our newborn screening community.

And it does require some thought. And I'm really excited about how we're going to move forward together in the near future.

Now, the comments -- just briefly commenting about the laboratory. Just a brief comment about the one that we couldn't remember, the homocystinuria screening method. We actually do have a manuscript that's been accepted that

talks about testing for homocysteine in a first-year method.

It does require some tweaking, so I know that while that publication is going to be coming out pretty soon this year, we are doing some tweaking because I know that one of the biomarkers, the C51, didn't do quite as well. So, we're looking at making some improvements there. And once we do that, we're going to look into seeing how we can transfer that method to the states.

Again, the funding opportunity that HRSA has provided to the states will go a long way into helping. It would send cases being able to implement that condition. But again, being able to work together is going to be very, very key in a good outcome.

Thank you.

NED CALONGE: Thanks, Carla.

And I want to tell the group I was reminded that the Evidence Review Group does publish their evidence reviews in Genetics in

Medicine. So, you took my suggestion long before I ever made it. I appreciate that.

I'd like to now turn to Natasha.

NATASHA BONHOMME: Natasha Bonhomme.

Two points I had up to the point in the conversation that was around evaluation. I think that the evaluation efforts can be really helpful. But making sure that what is being evaluated and the questions asked as part of that evaluation, however that would come up, actually tie back to what was the original intent of what was printed.

Especially if we're going to be evaluating things that were created quite a bit ago. I think sometimes we look at something and we wish it could be. As someone who produces a lot of education, I feel like, "Oh, I wish this was for providers," and it's like we could create that, but that was intended for families or what-have-you, right?

And the second point is, I think a lot of times we talk about "newborn screening" and

"rare" almost interchangeably. But to again remind this Committee that newborn screening is for every single child born in this country. And there is a lot that happens with newborn screening that is even before the diagnosis, before a family is onto that part of their journey.

And that there are a lot of opportunities to evaluate that whole piece, and thinking about where the communications happen on that.

And I bring that up because I also think it was interesting that -- obviously every subcommittee can determine what they want to focus on. A lot of it is around programs, and that makes sense. But there's a lot happening around newborn screening such as lawsuits and concerns around privacy that I think are quite urgent.

And again, I don't know if that's necessarily going to fit within any particular workgroup. But if they're looking at where the investments of time are going, it would be great to see where that might come up, even if it's

really educating the public about, what does it mean to be a program? And maybe there's some opportunity for across subcommittees. I can't remember if there are subcommittees or workgroups -- activity to be able to really meet the needs that see coming up.

NED CALONGE: Thanks, Natasha.

Margie.

MARGIE REAM: So, Margie Ream, organizational representative for Child Neurology Society.

A follow-up comment on the genetics and medicine, just as a part of the MPS II manuscripts that just went into print this week. And we're actively working on the GAMT manuscript. So, summarize the evidence review to disseminate the idea that it was reviewed and approved, or accepted for the RUSP.

So, as a child neurologist and member of the Follow-up and Treatment Workgroup, I'm very interested in the idea of patients-in-waiting. And patients-in-waiting are a phenomenon that's a

product of the newborn screening system.

And at least in the Follow-up and Treatment Workgroup, when we've talked about evaluating long-term outcomes -- for example, children identified at risk for cerebral ALD or Pompe -- the conversations often kind of move to the idea that that is under the clinical realm, it's the responsibility of the specialist or the advocacy groups that are particularly interested in that condition.

But I think there's also opportunity for kind of larger, a more global way of looking at it. But it's not just one disease now that has patients-in-waiting. And the incident of looking into the idea of harms versus benefit for the late-onset conditions is something that comes up with every condition that's being reviewed now, including yesterday.

So, I think it would really be bad to recover all funds available to look into the harms and benefits of patients-in-waiting that are a product of the newborn screening system. And

because the conditions are rare and require very long-term follow-up, I think it definitely extends beyond individual state or individual professional organization to look into that.

And also, the results of that data collection would be something that would be talked about with every condition that we review, just like it was yesterday.

NED CALONGE: Margie, do you have -- I don't mean to put you on the spot. But do you have ideas about what a system that crossed all those different groups might look like? Who might have -- you know, what to expect. I'm intrigued, but I just wonder if you've put thought into that.

MARGIE REAM: So, I have to admit, I'm not familiar with all of the potential options that might be under -- I don't know, under HRSA or MCHB. Because, you know, this is paternal and child health we're addressing, particularly the child part of that. I think it goes beyond MBSTR most likely because they are MBS. My understanding is that they are focused on slightly

shorter-term outcomes. But I might not understand that entirely.

NED CALONGE: Okay. Thanks. I appreciate it.

Bob Best.

ROBERT BEST: Yes. So, I just want to say that some of the tools that are being developed by CDC and HRSA and NICHD are really, I think, extraordinary and are going to be very powerful. So, hats off to everybody who's been a part of that.

I want to mention that the college, the American College of Medical Genetics and Genomics, has been pretty heavily involved in recent months and years developing evidence-based guidelines and doing systematic evidence reviews. And so, this is something that I think will complement the work of this group.

We have a new journal that has launched. So, you all probably know the Journal of Genetics and Medicine. And so now there's an open-access version called Genetics and Medicine

Open. And it's just now launching. And so, some part of the work of the open journal will be really to turn and focus toward therapy and publishing updates on therapies. So, that's one of the priorities of the journal.

So, I think, I would believe that the college would be a really strong partner for the work that this group is wishing to see move forward.

NED CALONGE: Thanks, Bob.

Shawn.

SHAWN McCANDLESS: I just want to respond to something that Dr. Ream said. First, I fully endorse her advisement that there be a focus on not assuming that there's no harms related to newborn screening programs, but that we seek real data about that.

But I also really feel like that -- I just want to respond to the term "patients-in-waiting." And I think in Krabbe disease in our discussion yesterday points that the patients that are not -- that are being followed up to determine

whether they develop disease or not, patients-in-waiting, they are patients. They have been given a diagnosis of, "We don't know what you have, but there's something there that needs to have MRI scans and frequent follow-up and neuro exams."

So, they're not patients-in-waiting; they're actually patients. And I think we just need to accept that directly and ask ourselves if those are really the targets of screening or not.

NED CALONGE: Margie, I think you wanted to respond.

MARGIE REAM: Yes.

Patients-in-waiting has been a term particularly applied in the literature to Pompe disease and possible late-onset Pompe. And I agree. Maybe that's not the best term with children at risk for Krabbe disease or childhood cerebral adrenoleukodystrophy.

And particularly in ALD, we know that those boys will eventually develop symptoms of disease. It may not be in childhood. It may not be brain disease. But they've all eventually

developed disease. And from my own personal experience taking care of babies that have been identified and newborn screened with that, what the families go through is really incredible.

To, you know, see how different families kind of deal with that uncertainty differently. And I think even if it was just ALD as a case-study kind of condition to follow up, but the follow-up is going to have to be for years because those children get from three until twelve, every six-month MRIs.

So, they are definitely getting lots of medicalization of their childhood experience, and for good reason, because the third that develop brain disease, if we catch it early, we can intervene. So, we'd love to talk about this more.

SHAWN McCANDLESS: Yes. I think most everybody here is familiar with where the term patients-in-waiting comes from. But it just always bothered me. Because if you're being told you have to come back every few months and you

have to have MRI scans every month, you're not a patients-in-waiting; you are a patient. And we just need to be straight about that.

NED CALONGE: Thanks.

Jennifer.

JENNIFER KWON: Well, to directly respond to Shawn, I would say that it's hard to be straight about it when we can't always give patients a diagnosis, at least a diagnosis that's meaningful to them that they feel like they can get some traction out of and that is intuitive to them.

So, for every condition, these indeterminate diagnoses have a different impact and have a somewhat different meaning. But I think that it is particularly difficult for families with a well-appearing child who has no biochemical or radiologic evidence of abnormality to be considered a patient.

We may care for them as patients. They are our patients. But their families are confused. And so, I was thinking what was

brilliant about what Margie said is that what crosses all diagnoses is a phenomenon of this cohort -- so in the CF literature or in the CF meaning, they talk about this "parking lot," right, for their indeterminate diagnoses.

And what I think would be helpful, I think there are many patients across diagnoses who would respond to the fact that they don't fit, that they just don't know where they fit. And they have particular anxieties and concerns that are not answered by the diagnosis that is in their medical record.

NED CALONGE: Thanks Jennifer.

Chanika.

CHANIKA PHORNPHUTKUL: I have two things. First I just want to echo what Dr. Best shared. I think many of us SIMD members are eager to work on all these evidence-based review, and currently I'm on two of them. And it's very exciting, and I really just see every time our members are really eager to contribute that way. So, I think that's one.

The other that I have been thinking about along what Shawn has said is this paradigm shift. And I think in medicine we are used to an algorithm. It's a yes or a no. And I think that this is an opportunity not only to study or, you know, look into the effect of, for lack of a better term, patients-in-waiting, or in the parking lot.

But also, how can we teach our new generation, medical students, residents, or existing health care providers that there is this new category. You know, I think we're so used to our ability to visualize, do physical exam, do the test, and make the diagnosis.

And now the paradigm has shifted, and that is not just newborn screening, but in population health. So, I think this may be an opportunity for us to sort of work with our public health colleagues in a really broad way. It may be broader beyond this Committee. But I thought something that's on my mind. So, I just want to share that.

Thank you.

NED CALONGE: Well, I really appreciate the robust conversation, and I apologize for letting it take a little bit of your lunch break away.

I think what I'd like to suggest, and staff and HRSA and I will circle back around. We will put together kind of a prioritization list that we can send out to Committee members and organizational reps to give us feedback on trying to decide what we're going to adopt as our activities or our topic groups for 2023.

We've done a lot of good input, and I think that's going to be the quickest and fairest way to kind of move forward on what we want. And then we could also, behind the scenes, figure out what resources we might be able to bring to bear to support those activities.

So, we'll do that asynchronously offline, and I would like to have us adjust the schedule a little bit to give you about 20 minutes to stretch and have a little nibblet to get you

through the afternoon. And we'll reconvene at about 10 minutes after noon Eastern Time.

Leticia, did you have any other comments before we break.

LETICIA MANNING: No. Just thank you for the conversation.

Actually, I do. I think we might be able to extend it for 30 minutes from lunch.

NED CALONGE: Okay. Okay.

LETICIA MANNING: I think we'll still stay on schedule.

NED CALONGE: Okay. So, that would be about 20 after. So, we'll be starting in at 20 after noon.

See you all soon.

BREAK

* (Whereupon, at 11:50 a.m., a lunch recess was taken, to reconvene at 12:20 p.m. Eastern Standard Time.)

NED CALONGE: Welcome, everyone, back. I'm going to just allow a small amount of time to see faces appear.

(Pause)

CARLA CUTHBERT: I'm here, Ned, this is Carla, even though you don't see my face.

NED CALONGE: Thanks, Carla. I appreciate that. Sorry I take that visual view.

CARLA CUTHBERT: No worries.

NED CALONGE: All right. Moving on the agenda. I remind you that the Committee received a nomination to include Duchenne muscular dystrophy, DMD, to the Recommended Uniform Screening Panel.

I briefly remind you about the nomination practice. The first step is for HRSA to conduct the initial review for completeness. After it's been determined the nomination package has the required components, the Nomination and Prioritization Workgroup reviews the information submitted in the package and provides the Committee with the summary and the recommendation as to whether or not the condition ought to move forward to a full evidence review.

The Committee will then vote to

assign or not assign the nominated condition to the ERG that conducts the review.

We received the nomination package for DMD in June of 2022. Today on behalf of the Nomination and Prioritization Workgroup, I will present the summary and workgroup recommendations to the Committee.

I'll cover this in the presentation as well, but I want to remind the Committee that at this phase of the nomination process, there are three core requirements for a condition to be considered, in addition to the information requested on the nomination form.

And those three core requirements are validation of the laboratory test, widely available confirmatory testing with the sensitive and specific diagnostic test, and a prospective population-based pilot study.

So, after the presentation we'll move on to full Committee discussion and vote.

I want to acknowledge that the fellow Committee members on the Nomination and

Prioritization Workgroup to review the nomination instead of a number of calls and a time coming up with the presentation that I will summarize today. So, I want to thank Kyle, Carla, Shawn, and Chanika for their work.

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NOMINATION SUMMARY: DUCHENNE MUSCULAR DYSTROPHY (DMD)

NED CALONGE: So, the nominator for DMD included Niki Armstrong and Pat Furlong, the Founder and the President of Parent Project Muscular Dystrophy, PPMD. The nomination is cosponsored by Muscular Dystrophy Association and the Duchenne RUSP Submission Workgroup, whose members are listed on this slide. Also, the advocate organizations are PPMD and MDA, as stated.

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NED CALONGE: To review, and you've

heard about some of this in the public comment period, DMD is an X-linked neuromuscular disease with progressive muscle damage and weakness in both skeletal and heart muscle. Primarily it affects males, although females can be variably affected.

It is associated with highly elevated levels of creatine-kinase. Diagnosis is based on genetic testing to identify these likely disease-causing variants in the *DMD* gene or muscle biopsy.

And by way of just convention, when we italicize DMD, it's the gene, and when it's not italicized, it's the condition.

So, deleterious variants in DMD are associated with other forms of disease, including Becker muscular dystrophy and DMD-associated dilated cardiomyopathy.

DMD is known to occur in approximately 1 in 5,000 live male births, and females with a pathogenic variant in *DMD* can be clinically affected, as stated.

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(Slide)

NED CALONGE: Clinically, DMD is a progressive neuromuscular disease of childhood. All patients with DMD experience loss of ambulation, followed by loss of upper limb use, progressive impairment of pulmonary function, and progressive cardiomyopathy.

Children affected often have significantly delayed developmental milestones in motor function, global developmental delays, and delayed onset of ambulation and other early motor skills.

It is noted that irreversible muscle damage begins as early as fetal life. And as you've heard, the diagnosis is typically made at four to five years of age, with loss of ambulation in early adolescence and death related to pulmonary or cardiac disease often in the patient's 30s.

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NED CALONGE: For treatment and

management, there are four FDA-approved exon skipping therapies available for DMD. These are considered as the standard of care for eligible patients, which are patients with an amenable pathogenic variant, who represent about 30 percent of the population of those affected with DMD.

These therapies are provided via weekly intravenous infusions. And the optimal age to initiate this treatment has not been established, though experts recommend offering it at the time of diagnosis even if corticosteroids are not yet appropriate.

Speaking of corticosteroids, they are also a standard of care and recommended to begin prior to the onset of physical decline. The average initiation of steroid therapy is 5.9 years. The optimal age to initiate steroids has not been clearly established. Current practice guidelines recommend discussing use at the time of initial diagnosis.

And as you heard, there are additional therapies in development that are in

various stages of clinical trials.

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NED CALONGE: Again, treatment typically begins as clinically indicated at the time of diagnosis, usually around four to five years.

There's no evidence on early treatment benefit because of diagnostic delay, clinical course, heterogeneous nature of DMD, and the rarity of this condition.

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NED CALONGE: Management also requires a multidisciplinary team led by a neurologist or physical medicine rehabilitation specialist, and the team includes cardiologists, therapists, genetic counselors, pulmonologists, orthopedists, and others.

Physical, language, and speech therapy and early intervention services have been shown to improve quality of life and early

functioning.

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NED CALONGE: So, remember the core requirements for nomination are a valid laboratory test. And there is a valid laboratory test available. Then a widely available confirmatory testing strategy with a sensitive and specific diagnostic test.

There is an FDA-approved screening test for creatine kinase MM-CK-MM. And GSP processing provides high throughput similar to other GSP tests used commonly in newborn screening.

Confirmatory testing requires next-gen sequencing, which debatably is not necessarily widely available, but is available.

And then there has been population-based pilot studies from New York, North Carolina, and the Zhejiang province of China.

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NED CALONGE: So, the core requirements are met. Moving up to ask the direct questions that are key questions to address in reviewing the nomination.

Here is the list of questions, and we will take them one at a time.

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NED CALONGE: Question 1, Is the nominated condition medically serious?

This is a health condition with morbidity that negatively impacts daily function and quality of life with all patients experiencing loss of ambulation, loss of upper limb use, and progressive impairment of pulmonary function, and progressive cardiomyopathy, with death relating to cardiac or pulmonary disease often occurring in the third decade of life.

Presentation is muscle weakness starting with calf hypertrophy and difficulty rising from the floor. Then ongoing delayed motor development, delayed onset of ambulation and other

early motor skills, frequent falls, difficulty with stairs. And the disease is known to be heterogeneous and nonspecific overall, but following this progressive model.

The conclusion of the group in answer to key question 1 is yes.

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NED CALONGE: Number 2: Is the case definition and the spectrum of this condition well described to help predict the phenotypic range of those children who will be identified based on population screening?

It's an X-linked disorder, primarily affecting males, but females can be affected. One-third of male individuals with DMD have a de novo pathogenic variant. And genetic testing identifies pathogenic and likely pathogenic variants. Also, muscle biopsy confirms the diagnosis.

There are other variants, including Becker muscular dystrophy that may also be

diagnosed and could benefit from early detection. And again, patients are typically clinically identified between four and five years of age.

The conclusion of our group was that the question 2 is answered yes.

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NED CALONGE: Key question 3 is, Are prospective pilot studies US and international from population-based assessments available for this disorder?

And these are listed on the slide with New York screening 39,495 newborns dating back to 2019. This is at the time of the nomination package. Four males were confirmed, and one female carrier.

In North Carolina, RTI ran the Early Check Pilot starting in 2020. There were 7,428 newborns screened, one detected with a pathogenic variant.

And in China, the pilot in Zhejiang province screened 18,424 newborns, with four DMD

newborns identified.

So, the answer to this question is yes.

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NED CALONGE: Does the screening test have established validity?

The committee spent some time on this particular question. There are screening tests for DMD. We talked about creatine kinase, the assay performed using the genetic screening processors available via PerkinElmer.

And then a second-tier test for confirmation, genetic analysis of the *DMD* gene via next-gen sequencing.

There are some challenges in the analytic screening validity area with different cutoffs for different ages complicating the question. There are false negatives known to be present in premature infants. But rather than address that issue or key question 4, we've move it to question 6 and concluded we would have

answered key question 4 yes.

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NED CALONGE: Key question 5: Are the characteristics of the screening test reasonable for the newborn screening system, among other aspects, a low rate of false negatives?

Here was another question with mixed information in the nomination package. For the committee to have addressed one of the things that we noticed in the way that we put the nomination package together is that there is a stressor or a worry of false negatives. And we wanted to assure folks that we believe key question 5 moving forward also needs to address false positives.

So, you can see the results for the New York pilot. The false negative rate was not reported. The false positive rate depended on whether you call it a positive screen or a borderline screen, and ranged between 0.1 and 0.9 percent, translating to positive predictive value again on those two groups, 11.9, or 1.5 percent.

The negative predictive value is not reported.

For the RTI pilot, the false negative rate was not reported. False positive rate was 0.7. Positive predictive value was 0.9 percent and no negative predictive value reported.

And Cure Duchenne-Brigham Women's Hospital supplemental DMD newborn screening ended up with zero confirmed, which does not allow for the calculation of the rates to actually discuss.

We realize that there will be newborns with high CK levels who don't have a pathologic variants, and the false positive rate is high given the low incidence.

So, that is a judgment call from the committee based on the false positive rates that have been presented on the predictive values given the low incidence.

If we, say, look at 4 million US groups annually and apply the New York or North Carolina rates, we would expect 400 to 500 positives to be identified each year.

At this point, the committee debated. And given the false positive rate in the setting of low incidence answered key question 5 No.

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NED CALONGE: Key question 6: Is there a widely available CLIA- and FDA-approved confirmatory test?

There is a test for the screening test. There are 196 labs that are able to provide confirmatory testing for DMD. Again, I think we ended up with a No for this in terms of FDA approval.

I will point out that, while this is a question in the Key Questions set, you know, this is an issue that the committee, thinking about its relative importance to making a decision about evidence review, is something that just is clearly something that the Committee can discuss.

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NED CALONGE: Are there treatment

protocols, FDA approved drugs, and is the treatment available?

And again, we talked about the treatment modalities in terms of exon skipping, corticosteroid therapy, and speech and physical therapy. And would answer that question yes.

We would point out that throughout the nomination evidence of treatment prior to usual clinical diagnosis is limited or unavailable.

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NED CALONGE: So, Key Question 8 is around clinical utility. And that is a very on-point question. We listed some issues in the nomination packet that are important to talk about.

Spectrum of disease. Do we know who's most likely to benefit, especially if treatment is onerous or risky?

I would start this discussion by talking about clinical utility a bit more. This

must include evidence and a discussion about the benefits of screening and the harms or potential harms of screening and treatment with enough specificity for the committee to judge whether a full evidence review is warranted.

We should have estimates based on available data of the frequency for all positives, the proportion of those positives that are false, and the processes and impact of determining these false positives. The frequency and magnitude of benefits associated with treatment and the frequency and magnitude of harms from treatment.

Finally, this answer should provide evidence that newborn screening detected cases will have better outcomes than those detected clinically or through another alternate detection strategy, such as screening that could be available through routine child health care.

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NED CALONGE: There are benefits from available therapy, as noted in the slide for

question 7. The benefits are significant and are described as delay in pulmonary functions, impact and delay in loss of ambulation. The longest follow-up reported in the packet was four years for exon skipping therapy and ten years for corticosteroids.

The committee concluded it is likely that the harms from therapy are outweighed by the benefits. However, we would point out that long-term data and data quantifying the frequency and severity of harms appear to be sparse.

Finally, the committee had remaining questions regarding variants of unknown significance.

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NED CALONGE: We recognize there are potential harms of a population-based screening program that have to be considered in determining the balance of benefits and harms in clinical utility. There was insufficient evidence provided in the nomination package of potential harms for

us to make a decision on clinical utility based on the balancing of harms and benefits.

There is insufficient evidence that newborn screening detected cases will have better outcomes than those detected clinically or through another alternate detection strategy such as screening through routine care when compared with what our committee is concerned with, population-based screening.

Putting all of these elements together, the committee came with the answer No for Key Question 8.

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NED CALONGE: Here is a summary of the Key Questions as the committee voted for them. And I just wanted the summary to be available for the Committee as a whole.

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NED CALONGE: I wanted to summarize the gaps that were noted by the Nomination and

Prioritization Workgroup. The reason for the recommendation to not be moved forward to evidence review includes, and perhaps most importantly, the limited evidence on whether newborn screening detected cases have better outcomes.

The benefits of treatment are based largely on expert opinion and not as much on published data. There was a lack of sibling studies, there was a lack of sited outcomes studies, and a lack of long-term treatment studies.

The workgroup discussed that newborn screening may not be the appropriate place to screen for DMD, as there are other screening timepoints that might be considered.

The gap for cutoffs for different ages provided challenge to the Committee, as the workgroup has been thinking about moving forward.

And in terms of treatment, the unclear benefits of early treatment, uncertainty around the benefits of exon skipping and long-term corticosteroid use, and questions about the age

and timing of treatment.

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NED CALONGE: So, the Nomination and Prioritization Workgroup makes this nomination that the Advisory Committee should not move forward the nomination of Duchenne muscular dystrophy forward for a full evidence review.

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(Slide)

NED CALONGE: I wanted to provide some additional thoughts. I would summarize that at this time the nomination group felt that the compelling evidence to consider adding DMD to the RUSP is not clear or has not yet been developed.

Now, in saying that, we did acknowledge, and I want to make sure the rest of the Committee, hears that we believe that this was an appropriate time to provide this submission to us and an appropriate submission to review. There is a test that can identify children. There is experience with population-based pilots. And

there is a new effective therapy.

Next slide, please.

(Slide).

NED CALONGE: As we discussed this particular item, we wanted to suggest it could be helpful for nominations to summary information that would allow the Nomination and Prioritization Workgroup to evaluate the estimated impact of screening some number of children.

For example, if we did 100,000 newborns, how many would test positive? Of those that tested positive, how many would test negative on the second-tier test or otherwise be determined to be falsely positive? What is the impact on these newborns and their families?

Of those truly positive, how many will benefit from treatment and what will be the nature and magnitude of that benefit? And of those treated, how many will be harmed by the treatment, and what will be the nature and magnitude of that harm?

Next slide, please.

(Slide)

NED CALONGE: Now, as we consider this nomination and that last slide, I wanted to assure the advocacy community that it is our intention to be changing the criteria for nominations to be approved for full evidence review.

But this nomination is accompanied with significant uncertainty about the likelihood that a full evidence review will reveal additional data that are relevant, allowing the Committee to make an informed decision.

We know that our field is changing, is changing with new testing approaches, new therapies, and more complexity in the conditions that we are considering. Our evaluation methods of nomination packets need to reflect this.

It is certain that the evidence for newborn screening for DMD and for other conditions will evolve and may well fill in the gaps where there is uncertainty.

Next slide. I think that is it. If

we can stop the slide share.

And I would like to open the session for discussion.

COMMITTEE DISCUSSION

NED CALONGE: I will prioritize trying to take comments and questions from Committee members first, and then turn to our organizational representatives.

Oh, and let me actually, Jennifer, since I saw your hand. Let me pause and just let Jennifer and Kyle and Carla and Shawn have the opportunity to make any comments on the presentation or other thoughts that you have.

Jennifer, since you raised your hand, I'm going to start with you. And you need to unmute. Thank you.

JENNIFER KWON: Were you wanting the people in your workgroup to make comments first?

NED CALONGE: That's correct. Thank you, Jennifer.

JENNIFER KWON: Yeah. I'm not on the workgroup.

NED CALONGE: Oh, I'm sorry. You're right. It was Chanika. My apologies. Sorry.

I'm going to start with Kyle.

KYLE BROTHERS: Thank you.

So, just looking, I just wanted to acknowledge that the Public Comment today raised what was to me new information. There was discussion of siblings. As far as I recall or could find, that information about siblings was not reported in the nomination. So, that's extremely useful information.

There was also a mention of a clinical trial testing early use of corticosteroids, assumingly with a comparison group of children not treated with corticosteroids early in their life, pre-symptomatically.

Again, a clinical trial like that would be extraordinarily helpful, especially if there are precise outcomes that can be compared in some direct way and not just descriptive.

So, there seems to be some disconnect there, right? It could be that simply these

things haven't been published yet and they need to be published or, you know, the trial just literally might not be over yet.

But I think it's really critically to point out that the nomination has the information that it has, and it could be that if there is more information or more information comes out literally in the next week, you know, that could really change things. So, I think this is a very fluid situation.

I think another point we're making is that we were concerned about false positives and the process that would need to be undertaken with a large number of babies in order to resolve false positives. You know, when you screen an entire population, 400 to 500 per year adds up really quickly.

But of course, if those can be resolved before they reach families and providers and can be handled at the first, second, or third tier of the screening process, then of course that really is a very different situation. So, there

still could be a significant amount of cost involved, but it's a relevant difference.

So, I think that's another piece of information that would be helpful to understand, is, can the false positives that actually reach patients and their experience with the health care system be prevented? Or is that sort of an inherent part of this practice, in which case that would be relevant to this kind of deliberation.

So, those are my initial thoughts.

Oh, and just, I don't think whether the FDA has approved a test or not is a primary concern and was not a factor in my personal decision.

You're muted, Ned. Sorry.

NED CALONGE: Thanks, and I tried to highlight that last point as we went through.

Chanika, you are also on the workgroup.

CHANIKA PHORNPHUTKUL: Yes, just briefly.

To echo what Kyle just said, I think

the other thing that we did think about was, what's the right timing? Since the testing, the first-year screening is CPK, and I'm just thinking, you know, children get CBC at one year of age.

Is that a time that that is something that could be considered as part of routine child care? So, that is something that we talked about quite a bit at the meeting. Thank you.

NED CALONGE: Thanks, Chanika.

Shawn.

SHAWN McCANDLESS: Thanks.

I would just echo what Kyle brought up about the fact that we heard several pieces of information this morning in the public comments that were not included in the nomination package and that were not things that were available to us.

And we had gone back to the nominators actually for additional information. So, there were two opportunities to present that. So, we presumed that those were not published yet

or were not at the time of the response. Those would be very helpful pieces of information to have.

The false positive screening is a very real concern because from the pilot data there were on the order of 50 false positives for every true positive case. Which means that if there are 500 true positives a year, we would expect to have 25,000 false positive cases a year.

So, that is a high enough number that we would really want to see -- first of all, all of those people would have to have DNA sequencing testing, which while it's widely available is not widely easily available or always paid for. So, there would need to be a mechanism for dealing with that issue.

But also, there just needs to be some more clarification about how easily those 25,000 false positive cases could be closed and families reassured that we just didn't see in the nomination package.

The last thing is that it also -- I

think we need to be really clear because you made a very good point, Dr. Calonge, that this is an excellent disorder that affects both males and females.

Although the data were less clear about females, based on who carries -- you know, the fact that two-thirds of the X chromosomes in the population exist in females, you would assume that there are twice as many females that have this X linked disorder, even if it's a milder phenotype, than there are males.

So, what was clear from the pilot study was that the screening test is not to identify female carriers. And I think we want to be really clear about whether that is the expectation of the nominators or not.

NED CALONGE: Thanks, Shawn.

Carla.

CARLA CUTHBERT: Yes. Again, a lot of what's been said I concur with. Kyle did notice we were talking about, you know, the public comment, I believe, was the two boys that were

described. And, you know, that would have been very helpful to have been part of our deliberation as well, especially when we asked for additional feedback from the nominators.

Again, it's just repeating much of what has been said, you know, from my point of view again having maybe about 20 to 25 screen positives is really difficult.

I don't think that as many of those would probably be referred for the sequencing, but dystrophin is a very, very large gene with, you know, lots of challenges about interpretation of the VUASs, and that does become a significant burden. While not on the states themselves, but for the follow-up, for the diagnostic programs as well.

So, again, we did agree that this is very fluid. We're looking forward to some of the studies that will be coming out in the near future. You know, we even thought that our thoughts might be a bit different if this package was submitted maybe six months to a year from now.

But again, with what we've been given and what we've asked for clarification, you know, the result is as Ned described earlier.

NED CALONGE: Thanks, Carla.

Jennifer.

JENNIFER KWON: So, I'm just curious what new treatment you were referring to when you said that in one of your last slides, the second-to-last slide?

NED CALONGE: I think we were talking about the gene therapy that we referred to this morning.

JENNIFER KWON: Oh, okay. Okay.

(Crosstalk)

JENNIFER KWON: And that is likely to be that we're waiting for FDA approval for in May? Okay.

NED CALONGE: Sorry.

JENNIFER KWON: Okay. I was just curious. Did the lack of a clear treatment in infancy, I notice that wasn't necessarily a key question, the lack of an intervention in infancy.

Was that a consideration at all of the workgroup?

NED CALONGE: Yeah. I think it was translated -- well, the way I would translate it and others can chime in -- was the issue about, is newborn screening, which would detect affected children in infancy, the approach, the best approach for addressing DMD?

JENNIFER KWON: And the only reason I bring that up is, you know, I thought it was excellent the list of questions you had for future nomination packages to address. And I guess I thought that wasn't necessarily clearly one of the questions. But I may have missed it.

Anyway, thank you.

SHAWN McCANDLESS: Can I just add to that? This is Shawn McCandless, Committee member.

I think the other question that was asked was, is there evidence that treatments that were before the time of symptoms leads to better outcomes? And I think that's where the question about the siblings that were recorded --

The committee was actually quite

surprised that with a condition this common, there was not published data about early diagnosis in siblings and the effect of early treatment and evidence showing benefit from early treatment.

So, those we think are our data that we think would be very, very important and helpful to have.

NED CALONGE: Thanks, Shawn.

Melissa.

MELISSA PARISI: Yeah. So, I had a question. I hope I'm not putting Michele Caggana on the spot. But I'd like to know a little bit more about those who screen positive and what kind of outcomes or follow-up analyses were pursued to help reduce or to address the high rate of false positives? I wonder if she could make any comments on that from experience at the New York State pilot study?

NED CALONGE: Melissa, Michele has recused herself from this vote.

MELISSA PARISI: Oh. Does that mean she's not allowed to listen to the discussion

either or make comments?

NED CALONGE: That's the way our current approach to recusals works.

MELISSA PARISI: Oh.

NED CALONGE: Yes. I didn't start with that, but because of the potential conflict of interest, Michele made the decision to recuse herself from this discussion.

MELISSA PARISI: Can anyone address this issue? Does anybody have any experience or feedback for us?

NED CALONGE: Again, it was something that we had hoped to have to be able to consider as we reviewed the nomination. And I think as we went back to the nominators for additional information, trying to understand all of the pathways, it was something we were hoping to get more information on.

(Pause)

NED CALONGE: Ash.

ASHUTOSH LAL: This is Ash Lal, Committee member.

I wanted to just yield back to the presentation this morning in the Public Comment section, expert from Nationwide Children's, that the biology of the disease lends itself perfectly to the condition to be screened at birth.

Because if we are seeing elevation of CK at birth, the process is started in the prenatal period. And the earlier the detection, one would assume for degenerative disease that the outcomes wouldn't be true. So, I think that if the screening has to happen, then either it should be part of the ...

And with the development of new therapies which look promising, I hope that they will be that that could be found forward for eventual inclusion.

Thank you.

NED CALONGE: Thanks, Ash.

So, I think one of the issues I want to just return to is the timing of evidence review such that there is likely to be published evidence that would provide sufficient information,

especially around this issue about early treatment as would be allowed by detection of it that could only be achieved through a compulsory population-based newborn screening.

That's the evidence that is important information in helping the Committee make the decision about the balance of benefits and harms with certainty. And I feel like we have a lot of indication that those evidence areas are being worked on and that there will be information that -- I can't predict the outcomes of the information. But that there could be information in again a very short timeframe.

Jennifer.

JENNIFER KWON: Well, I guess I would just respond to -- this is Jennifer Kwon, Committee member.

I would just respond to Ash's comment that I don't know if you know this, but I'm the Director of the Pediatric Neuromuscular Program at the University of Wisconsin. And it's a PPMD-certified clinic as well as an MDA-certified

clinic.

And no one is more familiar than me with the damage that is done to muscle by this disease. And I will say that I would -- you know, if we had an effective way to manage the disease very early in life, I think that would be great. But we really don't.

And even when we identified boys early in life, the lack of reasonable options to provide real modifications in the disease progression, I mean real honest-to-goodness real-world options as opposed to participation in clinical trials or a hope and a prayer that things are going to get better, I think that is really what is -- I think that's also what you should focus on, not just the fact that disease onset occurs, you know, is obviously occurring when these boys are born.

I think it leaves parents very frustrated to know how slowly treatments are evolving in this area. So, I guess I would disagree that just because a disease pathogenesis

starts early, that would be a rationale for newborn screening.

NED CALONGE: Thank you, Jennifer.

Melissa.

MELISSA PARISI: So, I wanted to make a couple of comments. And I wanted to really make the point that I think the data are not perfect and they never will be. And if we wait for the perfect randomized clinical trial, particularly one developed from a newborn screening pilot, we will be waiting a very long time.

I think from reviewing the data that there is emerging evidence around the benefit of early diagnosis and treatment, and particularly with some of the new therapies that are emerging. And I also think that we need to remember that for these relatively uncommon conditions such as DMD, which is more common than some of the conditions we've considered in this panel, the data are continuing to emerge.

I mean, the data as presented with the nomination in September, I mean, already more

papers have been published. And I think the fluidity of the emerging data suggests that the benefit of considering this for full evidence review may be warranted.

I'm not convinced that waiting is going to improve the outcome of the nomination, especially with the potential for new gene therapies that are under review and being considered by the FDA.

I'm also concerned that, given the three criteria that were established as necessary for consideration of moving a condition for full evidence review, which were met according to the summary of the report that was given, that those should be adequate for moving to full review.

It feels as if the Nomination and Prioritization Workgroup is setting the bar too high. It's now taking on the role of the evidence review itself.

From this morning's testimony, I don't think any parent should have to spend three years begging their pediatrician to pay attention

to their concerns about muscle weakness, motor development, and then large calves.

Especially now that we have some effective treatments that can at least ameliorate symptoms or slow the progression, using steroids, and even some treatments that show even greater promise through exon skipping technologies and through gene therapy for at least 30 percent of boys.

And I think that parents who described the differences between their children diagnosed at different ages, early versus late, they're quite compelling. But I dare any of you to get that published in the medical literature these days.

It's really hard to publish those individual case reports. And finding the hard data that document the difference in early diagnosis I think is actually quite challenging. Families and advocacy groups are struggling to do this.

So, I think the anecdotes are hard to

capture. The stories and the gray literature really do point to a compelling story that early diagnosis will improve outcome. And in fact, that is the entire premise of newborn screening. I don't think we have encountered that many conditions where we said, "No, it's better to wait before diagnosis," particularly with a condition like DMD, in which we know that the muscle degeneration starts prior to birth.

From condition after condition, even those with later onset, we have found that there have been benefits from knowledge of early diagnosis. And I think that's the case for Duchenne.

And then finally I wanted to say that I've looked at the nomination and some of the emerging evidence. And maybe I didn't do as thorough a job as the N&P Workgroup. But I found examples of publications that showed that early treatment, as early at least as six months of age, showed improved outcomes for boys that underwent those treatments.

There are a number of papers that are emerging, I just did a literature search this morning, that show that some of the exon skipping modalities are being used in boys as young as six months of age. All of these point to the emerging evidence that early diagnosis and treatment will improve outcomes.

There was a paper that was cited in the nomination packet that was actually a platform presentation at the American Society of Gene and Cell Therapy, which has since been published, and it's by Dr. Waldrop, who gave testimony this morning about the value of early treatment with some of these emerging therapies, and in particular gene therapy, which has now had some publications that are associated with it.

And I think that there's quite a bit of evidence from the Muscular Dystrophy Surveillance, Tracking, and Research Network, the MD STARnet, which has been funded by CDC over a number of years, that suggest that the value of early diagnosis and treatment is quite beneficial.

A paper that was just published in 2022 showed that the time interval between the first signs of Duchenne and diagnosis of Duchenne remain unchanged. It takes 2.2 years. So, even with all of the efforts that we have made to try to improve the earlier diagnosis of Duchenne muscular dystrophy, on average boys are still getting diagnosed between four and five years of age.

And that's just too late for these families who really are counting on some of the benefits of treatments, whether they be steroids, physical therapy, or even just being able to plan for the life of their family moving forward.

There's another paper that has been published in 2022 looking at selective clinical and demographic factors and all-cause mortality among individuals with DMD, again from the MD STARnet. And this paper again shows that glucocorticoid use is really important and that individuals who come from non-Hispanic/Black families have a later stage of diagnosis and they

have poorer outcomes.

Finally, there's a paper that has just been published in January of this year on racial and ethnic differences in timing of diagnosis and clinical services received in Duchenne muscular dystrophy, again from the MD STARnet.

And their conclusions are really that there are racial and ethnic differences at ages of diagnostic and treatment milestones, and most significant delays of five to seven milestones. These are milestones with regard to diagnosis and treatment for non-Hispanic/Black individuals, which are attributable to later initial evaluation and diagnosis.

So, in my opinion, in looking at the evidence, I think this is an equity issue and that newborn screening, consideration of adding newborn screening to the RUSP, and at least giving it the benefit of a full evidence review, would allow us to take a deeper dive into some of these papers that have been published more recently.

So, I think that there is emerging evidence. And I think waiting on another nomination is not really going to save us that much time. And I think the time is now to consider this for full evidence review.

Thank you.

JENNIFER KWON: This is Jennifer Kwon. And I'm going to just butt right in. I know Bob Ostrander is about to strangle me.

But just from the point of view of a person who would like to treat her patients earlier, and who is very familiar with the effects of all of the treatments available for Duchenne, and also really quite familiar with the early treatment trials that have been offered -- early treatment, twice-weekly steroids, early treatment with exon skipping.

I would love to see some follow-up data from those trials. We haven't really seen those. And the fact about outcomes is that there's no question that diagnosing earlier and treating earlier adds years to ambulation, which

has downstream effects on overall health and survival. There's no question about that.

But the barriers, the equity barriers you talk about medical care, which could be overcome by early diagnosis -- yes, all boys would be diagnosed at the same time -- I have boys who go to public health clinics who come from less advantaged populations, and I worry that despite a reasonable time to diagnosis, their outcomes are still not that much better because of other equity issues that they face.

So, this is a very complex problem and a complex issue. I actually think that the data for early treatment and the positive data that we're hoping for from gene therapy may be better reviewed with another nomination. I'm not sure that starting the evidence review clock now and giving them nine months will actually be able to capture more.

I worry that it would be bad for the nomination of this condition, in which I see so many issues and problems that I would love to

solve.

Thank you. I won't talk any more.

(Pause)

JENNIFER KWON: I think you're muted? I'm sorry. Am I muted?

(Pause)

NED CALONGE: Robert.

ROBERT OSTRANDER: I'm finally unmuted here. Thanks. I'm trying not to act too impatient, Jennifer. It's my ADD that I don't treat. So, don't mind me waving on. From the time I was in second grade, my classmates said I needed to sit more still.

Well, I have a couple of questions. One is, during the presentation, although your comment was that there was no evidence that early treatment changed things, I thought the definition of "treatment" was pretty narrow if you're just talking about corticosteroids and exon skipping therapy. There are non-pharmacologic, non-disease directed treatments that make a difference.

And you stated in the evidence that

there was clear evidence that when people get started with support services and physical therapy earlier, bracing, all sorts of things, that indeed it delayed loss of function.

So, I think when we think about treatment, we have to think about treatment in total.

Secondly, we always have this discussion about, is there benefit to pre-symptomatic treatment? And with this disease, we have to say, is there benefit to pre-diagnosis treatment? Because symptoms precede diagnosis by a couple of years.

And if one were to make the diagnosis earlier, even if you were going to do the watchful waiting like we talked about with the less severe forms of Krabbe, early symptoms would be the initiation of treatment, and that late symptoms, which I think is where we are now with this disease, I think that needs to be investigated by a good, thorough review rather than necessarily waiting for any more, you know, tests of

biological interventions.

I would be interested in your thoughts on that.

I will comment that delaying -- even if we don't delay disease progression with these interventions, if we prolong or stabilize function for a period of time, that's not a novel concept. I mean, again I treat adults, right?

I have a lot of folks with Alzheimer's disease, and there is no treatment that modifies the progression of that disease. But donepezil and some of the other treatments stabilize function for a period of time. And we all think that's very worthwhile, to stabilize function for a period of time.

But I think to say that there's no benefit because it doesn't -- we don't have proof that it affects disease progression, I don't think that's a reason to say that there's no benefit from early detection and screening.

My other couple of questions are, well, this one is just purely a biological

question. But since the treatment doesn't have to be instituted right away, is one of the ways to deal with the false positives just to retest in a couple of months? I mean, some of those CKs I would expect would come down, and so you can remove those folks from the pool that needed sequencing pretty readily.

I guess that's all the questions I have for the moment.

NED CALONGE: Yeah. I think, Robert, I would say that we considered a number of those issues. I think changing the screening paradigm requires evidence. And I understand that all of your -- I mean, even right to your suggestion. If there is time to wait or since there is time before symptoms occur, it does raise an issue, are there other approaches that are screening the entire population through newborn screening in a public health approach? That might be a reasonable alternative.

I don't know if Shawn or other, or Chanika or others want to weigh in. But I do want

to say that we considered a lot of questions in coming to the conclusions that we did.

Scott.

SCOTT SHONE: Scott Shone, org rep from ASTHO.

So, wanted to focus my question for you for the workgroup on your answer to questions 5 and 6. I don't feel like I'm in a position to comment on 8. There's been a lot of conversation around that.

But I know Kyle did mention that the answers to the question 6, which is, is there a widely available creatine or FDA approved confirmatory diagnostic process is no, didn't weigh in. I do think it's important to realize that for rare diseases, laboratories develop tests that are hallmark of need for laboratories.

And so, I hope that -- I mean, 194 labs that actually provide some sort of confirmatory test is a large number to me. And I understand the NGS comment, but we often talk about readily available that's becoming.

So, I think it's a little -- I think it just needs to be dealt with caution when focusing purely on a yes/no whether there's an FDA-cleared, and not approved, but FDA-cleared test for a diagnostic process.

I think that the system got lucky that a diagnostic manufacturer like PerkinElmer got ahead of this as a screen test and got that FDA cleared early enough to be able to be used.

But I really wanted to ask if the workgroup took into account that the pilot studies that were cited were in fact just that -- smaller-scale pilot studies. While large in size with, you know, almost 37,000 and 7,000 in two different states, the pilot studies inherently have cutoffs that are more conservative in an effort to capture more babies who identify where they would land in the confirmatory and diagnostic process.

I know the RTI pilot specifically was intended to cast as broad a net as possible to figure out and help newborn screening systems see what we are going to face when this becomes more

population based. So, I think it is dangerous to ascribe a PPV from a sub-population pilot study to a population-scale implementation.

Moreover, we routinely have to deal with age-related cutoff and other demographic-variable cutoffs with all of the ASQs we currently run. SCID, and I know, Ned, is a common citation for you. SCID is with issues with preemies, micro-preemies. And we all have either cutoffs or algorithms established with our consultants, with our immunologists to face that with congenital hypothyroidism and congenital hemihyperplasia.

Some states have three or four related, weight-related cutoffs of age-related cutoffs to address for that. But I think it needs to dealt with caution. I just would ask the workgroup to see how much of the cutoff concern was related to pushing back on this.

Because there should be good data within these pilot studies. Maybe it just wasn't presented, is my question, of why cutoffs were set where they were. And if they were adjusted

differently, where the resulting false positive rate may have landed that would have made the workgroup more comfortable.

NED CALONGE: Yeah. I appreciate those comments. And the workgroup had available what we had in the nomination package. But I think it's good comments to keep in mind as issues about how pilot studies do tend to cast wider.

I think we've had a lot of good discussions. I think there are as good, I would say, diversity of opinion among the voting Committee members.

And at this point, I'd like to entertain a motion to move DMD forward in evidence-based review. And then take a roll call vote.

(Pause)

NED CALONGE: Ash.

ASHUTOSH LAL: I support the motion to move forward to evidence review.

NED CALONGE: Ash has -- I'm taking that, Ash, that you move to move the condition

forward to full evidence review.

Melissa.

MELISSA PARISI: Second the motion.

NED CALONGE: The motion has been moved and seconded.

Again, the motion is the Advisory Committee recommends to move DMD forward to evidence-based review.

VOTE

NED CALONGE: I'm going to do a roll call vote. Please respond by saying yes or no, or "I abstain."

Starting, Kyle, you always get to go first.

KYLE BROTHERS: That's okay. Yes.

NED CALONGE: Michele Caggana is recused.

Jannine.

JANNINE CODY: I vote yes.

NED CALONGE: Carla.

CARLA CUTHBERT: No.

NED CALONGE: Jane.
(No audible response)
NED CALONGE: Jane, I don't hear you.
(Pause)
JANE DeLUCA: Can you hear me now?
NED CALONGE: Yes.
JANE DeLUCA: No is my vote.
NED CALONGE: Thank you.
Kellie.
KELLIE KELM: No.
NED CALONGE: Jennifer.
JENNIFER KWON: No.
NED CALONGE: Michael.
MICHAEL WARREN: No.
NED CALONGE: Ash.
ASHUTOSH LAL: Yes.
NED CALONGE: Shawn.
SHAWN McCANDLESS: No.
NED CALONGE: Kamila.
(No audible response)
NED CALONGE: Kamila, you are muted.
And I still don't hear you.

(Pause)

NED CALONGE: Okay. I'm going to skip Kamila for now.

Melissa.

MELISSA PARISI: Yes.

NED CALONGE: Chanika.

CHANIKA PHORNPHUTKUL: No.

NED CALONGE: Kamila.

KAMILA MISTRY: No. Can you hear me, Ned?

NED CALONGE: Yes. Thank you, Kamila.

KAMILA MISTRY: Thank you.

NED CALONGE: And I vote no.

The vote count is four yes, nine no, and one recusal. So, at this point the vote is to not move forward.

NED CALONGE: I want to thank the Committee for a great conversation and consideration. We realize that the nominators were hoping for a different outcome. I'll provide a letter that summarizes the information for the

Committee to reconsider the nomination to the RUSP.

I would point out that there has been such a good conversation, my hope is that the nominators are not discouraged, and that as the evidence, even things we heard today, become part of the evidence body or will become part of the evidence body, the nominators will consider resubmission of the nomination.

And, Carla, did I not call you again?

CARLA CUTHBERT: No. I just wanted to comment that I wanted you to say what you were going to say, but possible perhaps to have some kind of expedited review of their package. I know that we'll do what we need to do to review their package if they get data that are appropriate and perhaps that meet the needs.

NED CALONGE: Well, I would hope that. And a lot of it depends on -- well, I hate to say anything. It's as dangerous to make predictions, especially about the future.

CARLA CUTHBERT: Right.

NED CALONGE: We've talked about the gaps. I would think that the nominators will hear that and we can consider renomination at any time. I think there's an advantage that the current N&P workgroup has spent a lot of time on this issue and would be able to do a review in a very timely fashion.

NED CALONGE: Okay. So, I would like to move on in the agenda.

HRSA STATE INTEROPERABILITY PROGRAM

NED CALONGE: And I would like to apologize to our presenters. It's always the risk of presentations that come later in the session. But it doesn't take away how excited we are to hear about the HRSA State Interoperability Program that's to support state programs.

We have the three grantees that will present on their projects, Dr. Craig Newman, from Altarum. He's the Project Director for the HRSA-led Innovations in Newborn Screening Interoperability Project, with 17-plus years of

experience in health care data interoperability and the Co-chair of both the HL7 Public Health Workgroup and the V2 Management Group.

We will also hear from Radley Remo, the Project Manager of the Newborn Screening Laboratory in the Bureau of Public Health Labs from the Florida Department of Health. He's working to implement ETOR for the laboratory.

Also from Florida, the Department of Health, will be Juan Vasquez. Mr. Vasquez is the service provider/manager at the Florida Department of Health's Data Administration Team, Integration Broker Services. Currently collaborating with the newborn screening program on electronic testing orders and results, modernization, matching data between lab information management system and Florida Vital Statistics.

And then finally, Andy Rohrwasser from the Utah Department of Health.

And I will turn these things over starting to Craig.

CRAIG NEWMAN: All right. Thanks for

the opportunity to talk to you about data interoperability for newborn screening programs.

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CRAIG NEWMAN: I don't have any conflicts of interest to disclose.

One more slide, please.

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CRAIG NEWMAN: So, let's start with the definition of "interoperability" because it can mean different things to different people. But it's basically about the ability of systems to exchange information in a meaningful way across boundaries, whether those are organizational or jurisdictional.

And key to this is ensuring that the meaning is not lost as data are shared and that information from multiple systems can be compiled and used independently of where it originated.

But the larger question is, why do this? Why does it matter?

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CRAIG NEWMAN: And the answer to that is so that we can take better care of both individuals and populations. It's about connecting people with their data and with each other.

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CRAIG NEWMAN: There are a lot of things that enhanced data sharing can help us with. There's the need to improve communication with newborn screening partners so that there's accurate and timely access to screening results available for our public health programs, including reliable count of children being born in a jurisdiction to ensure that all newborns are accounted for and supported.

The screening data then form the basis of all that newborn screening programs do. And so, in order to provide these supports and services to affected individuals. And everything from quality assurance to patient safety to

answering critical health equity questions, we need that reliable, verifiable, and auditable data that form the foundation of a strong continuum of care for these children and their families.

Then finally, in the age of patient empowerment and communication, the free flow of data between providers, programs, and families is a necessity for longitudinal care across a lifetime and in all facets of an individual's life.

But hopefully, these goals aren't new to anyone here. There have been a large number of community members that have been highlighting these needs and objectives for many years. And we're thankful that all of those prior discussions have led to the program that we're going to talk to you about today.

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CRAIG NEWMAN: So, despite the importance in successive newborn screening programs, there are still significant barriers to

ensuring that relevant data are exchanged easily between systems. But we do know from work in other public health programs that electronic data exchange has the ability to revolutionize how data are collected and used. And this makes the effort to achieve interoperability well worth it.

But to effectively address the current gaps in interoperability, our state public health programs need assistance and resources to evaluate their current health information technology infrastructure to understand requirements and best practices and to develop a plan to support improved interoperability.

So, to meet this need, in 2020 HRSA launched the Innovations in Newborn Screening Interoperability Project, or INDSI.

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CRAIG NEWMAN: Comprised of a diverse group of experts in newborn screening interoperability and evaluation, our INBSI team works directly with jurisdictional programs to

build the foundation for improved data sharing.

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CRAIG NEWMAN: Our aim is really to assist in addressing the gaps and the barriers in the current data exchange ecosystem, and we do this by helping these programs understand their current interoperability readiness and to develop that roadmap to achieve their goals.

We also provide training to build a solid foundation of understanding of the technical and operational aspects of interoperability. And finally, we promote collaboration between programs and subject matter experts.

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CRAIG NEWMAN: Our technical assistance team works directly with newborn screening programs to develop a readiness assessment which documents their current state. We work with the program staff to understand the unique needs of the jurisdiction, exploring a wide

variety of different things, from technical infrastructure to resource capacity.

And this readiness assessment then forms the foundation for the development of an interoperability roadmap to document strategic approaches and tangible next steps to help programs identify and reach their data-sharing goals.

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CRAIG NEWMAN: We also provide educational offerings that fall into three major buckets. We offer a monthly webinar series across a variety of technical and operational subjects. As well, we have a library of on-demand trainings that cover things in short and easy-to-digest bites, from technical topics to kickstarting programs to other federal objectives that public health programs can take advantage of to advance interoperability.

Finally, we offer state programs the opportunity to participate in our project ECHO

program. This is a virtual learning collaborative where program staff have the opportunity to learn from and interact with our interoperability subject-matter experts and present real-life issues that they're encountering to receive input and feedback from their peers and our experts.

Our diverse set of resources and opportunities means that there's something for everyone regardless of their current level of understanding and interests. And as such, we've had participation from virtually all jurisdictions across the country in one training forum or another.

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CRAIG NEWMAN: Here we show the roster of states that we're directly interacting with one-on-one either through our technical assistance arm or as part of our project ECHO series. And as you can see, many of the states are participating with us in multiple ways.

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CRAIG NEWMAN: As we've worked with the states, we've found that programs are facing a large number of common challenges when it comes to implementing data-sharing with providers and other partners. And these align into some larger themes such as community and communication.

Newborn screening programs are often siloed within a jurisdiction and aren't always communicating, sharing, and learning from each other. And this can make it difficult to build up a strategic vision for newborn screening data sharing.

Resources. Programs often lack the technical and practical experience with interoperability. When that knowledge exists, it's often not institutional, but in the heads of a small number of people with a lot of different demands on their time, meaning that programs don't always have access to the critical knowledge that they need, and that staff turnover tends to hit very heard.

And then finally, inertia. Simply put, it can be hard to get started. Leadership, both within the jurisdiction and with submitters is often difficult to get, and reliable, sustainable funding is often lacking. And finally, the need to accommodate non-optimized systems and workflows can make it challenging to take the first step.

But we're seeing people make progress across the country.

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CRAIG NEWMAN: So, what are some of the lessons learned by these early adopters that all programs can use to overcome the challenges? Well, what we've seen is that newborn screening programs that work together and harmonize their activities and expectations fare the best.

Health equity is an important priority in the country, and programs have been leveraging this to advance interoperability and identify gaps in care and missing data to address

those issues.

Finally, as a community we need to broaden our thinking on what data exchange means. Who needs to be sharing information? It's not just about receiving data from hospital, although this is certainly an important piece. It's about integrating with vital records, identifying new programs to share data with, exploring new technology and new paradigms for sharing data with nontraditional sources and more.

Programs need to think broadly about what it means to share data and then advocate for their needs as new interoperability approaches are being developed within their jurisdictions.

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CRAIG NEWMAN: So, we're already seeing a lot of state partners take action to make interoperability a reality. They are applying their understanding and recommendations in taking those tangible next steps. They're identifying ways to add or strengthen the resources they have

at their disposal.

We're seeing them work with colleagues in other states on common issues or seeking out other public health programs to share approaches and resources. And they're using the learning opportunities they have to build that strong foundation of understanding.

More states are now ready to take those next steps toward achieving interoperability. And working together, we can improve the flow of information and provide our newborn screening programs with the tools and the data that they need to supported impacted newborns and their families.

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CRAIG NEWMAN: So, in addition to our tremendous INBSI team, we couldn't have done this without the guidance and support from our advisory board and Project ECHO faculty members. So, we'd like to give them a special thanks for all that they do for us.

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CRAIG NEWMAN: Thank you for the opportunity to join you today. And if you do have any further questions, please do reach out to us.

Thank you.

NED CALONGE: Thanks so much for your excellent presentation.

I would like to maybe save questions until we have all of the presenters present. So, if folks can write down questions that you might have.

Let's turn to our colleagues from the Florida Department of Health.

And please identify yourself as you start speaking.

JUAN VASQUEZ: Thank you. Good afternoon. My name is Juan Vasquez. I'm the Service Provider Manager for the Integration Broker Services Team at the Florida Department of Health. And we work closely with the newborn screening program at the Florida State Lab,

specifically with Radley.

Radley, if you would like to introduce yourself?

RADLEY REMO: Good afternoon. This is Radley Remo with the Florida Department of Health. I also want to thank you guys for giving us the opportunity to talk to you about what we're doing here in Florida.

JUAN VASQUEZ: Thank you.

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JUAN VASQUEZ: Next slide, please.

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JUAN VASQUEZ: Okay. So, a brief outline of our presentation today. We'll be speaking with you about the self and readiness assessments that we conducted, and then also talk about newborn screening electronic orders and results, and newborn screening data quality -- the data matching that we're proposing and working on with Florida Vital Stats.

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JUAN VASQUEZ: So, as we conducted our self and readiness assessment, we had to understand first that we needed to get the insight from all of the staff at the newborn screening program at the lab. So, we did staff interviews.

We also did provider and training partner focus groups to get feedback from all of our stakeholders. So, we set up some focus groups to find out what to talk about, not only data flows and interoperability, but the workflows and how the data flow applies to the day-to-day workflow that the providers and training partners encounter so that we could get a good picture of, one, where interoperability exists, but two, where interoperability could either be introduced or improved upon.

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JUAN VASQUEZ: So, with those results, we used them to work on our interoperability plan for the state newborn

screening program. And so, we were able to identify opportunities for interoperability and/or modernization. As we spoke about earlier, we do have existing interoperability within the processes that are available. However, there may be opportunities for modernization, to use different tools, or to implement newer standards that help with efficiency.

And so, we took those workflows and data flows that were shared to us by the staff and by the trading partners and developed to be recommendations.

And then lastly, we take that to develop -- well, we added to that to make sure that we're considering the leading standards and modernization tools.

So, for example, some of the needs and opportunities that were identified as part of the focus groups and as part of the interoperability plan was that our trading partners mentioned that they would like to see HL7 electronic orders and results as part of the

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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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,

department and program stakeholders. So, we had the Bureau of Public Health Laboratories at the Department of Health Division of Disease Control; the Office of Information Technology and the Data Administration Team; and then also Children's Medical Services, which is the newborn screening follow-up program.

So, those are the programmatic and department stakeholders.

And we had to look at the technical stakeholders. We work with RUVOS, which is the provider for the Integration Broker Services Team, with the Data Administration Team at the Florida Department of Health. And we also work with PerkinElmer, the lab information management system for the Public Health Laboratory in Florida.

And then of course again working with our trading partners, birthing centers that use the various processes at the Florida Department of Health.

We also had to look at requirements gathering, project planning, and then training.

So, as part of this project, we've been conducting quarterly training for all of the newborn screening staff.

And our training is a mix of partnering with INBSI, who just presented with us. We look at the topic that we're covering that quarter and provide, or share, the links for the presentation on that topic from INBSI. All of our staff have an account with INBSI, and we encourage them to take that training.

And then we customize a Florida-specific training on the topic and how it applies to the Florida processes. And so that's how we are conducting training for all of our staff.

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JUAN VASQUEZ: So, one of the recommendations that came out of the interoperability plan is to implement electronic orders and results. So, we first took a look at the infrastructure, the existing infrastructure and what infrastructure improvements needed to be

made. And then to understand the requirements, but from both sides -- one is from the lab information management system, and then also from the providers, the trading partners.

Then we worked on a design, and are now currently working on coordinating that implementation. And we'll be conducting a pilot this year.

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JUAN VASQUEZ: So, here is an example of the as-is readiness assessment that we did. Florida has a diverse set of trading partners from small facilities that do not have electronic health record systems that use an online portal. For example, here on the top right you'll see a web order system. And they're able to submit their orders that get routed to the PerkinElmer directory within the lab information management system.

We also have another process where flat file orders are sent using MoveIT from the

hospitals to the LIMS. We also send results previously through a fax system, but now we're using MoveIT to deliver those results.

We also have HL7 electronic orders and results from the hospitals to the LIMS. But it's not end-to-end. It's HL7 forwarded. That's converted to a flat file, and then the results come in as a flat file converted to HL7. And lastly, we still do have many providers who use manual specimen cards.

So, we spent a great deal of time not only looking at what these existing processes are, but speaking to our providers, how they think they can be improved or how they think they can come, add more interoperability to how they submit orders and receive their results.

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JUAN VASQUEZ: And so, out of that, this is where we have our implementation project. It will be working with the Integrity Intelligent Messaging platform, where the hospital is able to

submit their HL7 orders. And then as it moves through the Integrity platform, it has data validation for data quality. There's also inline validation and online validation, anomaly detection with notifications and alerts to the program.

And so, then that order goes, it's sent to the LIMS. And the orders come back, again ensuring that there's data validation, anomaly detection, and alerts and notifications to ensure that the hospital is receiving these results to the specifications that they need to get it into their EHR.

So, this is the process that we will be highlighting with some of our trading partners throughout this year.

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JUAN VASQUEZ: We also have another project that we'll be implementing and that's the data quality project. Originally a requirement of this project is to match 100 percent of newborn

screening records with Florida's vital stats birth records. And the original design or proposal was to make sure that all newborn screenings also had a vital stats birth record.

However, as we interviewed and held our focus groups with the staff, we realized that the bigger need -- I don't want to say the more important need, but the need that was important to the staff was for data matching.

So, our staff in carrying out their data quality activities within the lab information management system, they had to confirm birth, date and time, medical record numbers, mother's address, and birth hospital. There's actually some more, but these were the most important to them at the time.

And they had a need to confirm or get the correct information from Florida Vital Stats. So, their request was to see, is there a way to have interoperability between the Florida Vital Stats database and the newborn screening LIMS database to be able to conduct matching and give

alerts and notifications when there was a discrepancy in those data?

As we work with Florida Vital Stats, they actually had the same -- the original request, which was for matching of missing records. And so we're able to do a bidirectional matching process where vital stats could get the information that they need, and then the newborn screening program is able to confirm the data that they are needing for their records.

So, we did conduct a design process with all of the stakeholders.

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JUAN VASQUEZ: So, if you look here on the left-hand side -- I know it may be a little bit blurry -- can you guys see my mouse here? Oh, no, because we're on the other presentation.

So, we have three ways in which orders come in to the process. If you look at the top at the manual card entry, and so you'll see that -- when you see a circle with a check, that's

where there are data quality checks going on. We have the web order and the HL7 flat file, which go into a holding table, and then the card is scanned. It also goes into the LIMS at that time. See that at the bottom.

At the top there's manual data entry into the LIMS. Once all of that data is in there, we confirm or do a critical field data validation process where we're ensuring that the information that is on the card is also the same information that was input or received by the LIMS.

However, as part of that process, they're confirming whether what's on the card is on the LIMS, but you're not confirming whether that information is correct. You're just confirming that it's the same at both points.

So, that's where the program identified that they would like to be able to match with vital stats to ensure that what's in vital stats is what's on the card and on the LIMS. And so you'll see on the righthand side the proposed high-level process is to conduct 100

percent matching with vital stats and LIMS and then be able to create an alert and notification so that the team could follow up and confirm which is the data that's going to be used.

So, that process is the project that we're developing now for implementation.

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Well, that's it right there. If you have any questions, we'll be available at the end.

Thank you.

NED CALONGE: Thank you.

We can now turn to our colleagues from Utah.

ANDY ROHRWASSER: Hello. Can everybody hear me?

NED CALONGE: Yes. Thank you.

ANDY ROHRWASSER: Great. So, I'm Andy Rohrwasser. I serve as a laboratory director in Utah, and my domain expertise and passion is newborn screening, making the newborn screening system scalable and really think about what we need to do in terms of infrastructure development

to achieve these goals.

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ANDY ROHRWASSER: So, Craig did an excellent job describing providing a high level, giving a high-level overview of these models. We are, of course, super-super thankful for the HRSA funding we received.

Our work is motivated by really aspects of economies of scale and accountability. So, when I say economies of scale, we are currently thinking of expanding newborn screening. We are thinking about how we can add anywhere between four and ten additional disorders to our panel.

And in order to do that, we really need to think through how we can do that, how we can do that from the IT systems, how we can introduce mechanisms of accountability, and how we lay the foundation for a scale of a long-term fall-out solution.

So, when we think about data

interoperability, we think about several distinct phases. So, we have the device management phase. That is the phase that describes the program and provider interactions prior to collection of the screen. So, device registration, inventory management, device order and use, and then collection of specimen, so device logistics.

In the pre-analytical phase, that's more common, right, that we have questions with regard to accurate demographic information collection, timely collection of the newborn screen, timely transfer to the laboratory, registration at arrival, and then the communication phase with provider regarding unsatisfactory specimens. So, prior to the actual testing.

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ANDY ROHRWASSER: In the analytical phase, data interoperability comes in when we think about general LIMS function. How do we ensure a cloud functionality interoperability so

that we have agile web-based systems that can help us in COOP scenarios.

We need easily configurable LIMS solutions, so internally and externally. And we need to have easy connectivity with diagnostic reference laboratories and third parties.

And especially after listening to this session, this is more and more important that we think about this, as we are hit with the introduction of next-generation sequencing approaches. We need to have solutions to be ready to deliver on these goals.

And then of course there is a post-analytical phase that's follow-up. As we know, short-term follow-up and results dissemination. We need reference laboratory connectivity. We need EHR connectivity. And then we need long-term follow-up solution for automated, as well as ad hoc emergency situations.

And then, of course, we need key performance indicators capabilities to communicate with internal and external stakeholders.

I am accountable to the legislature in terms of, I get questions asked when we are below 99-point-whatever percent of newborns not being screened. So, this is really, really super important.

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ANDY ROHRWASSER: So, device management, cash/revenue cycle support solution, laboratory information management system solution, chain-of-custody environments, and then customer engagement. These are the broad categories which we think about when we think in terms of support requirements.

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ANDY ROHRWASSER: I don't want to -- obviously this is very complex. And I want to highlight maybe on a few examples what we mean, how we approach that. So, I want to show you an example of a chain of custody environment. And then talking a little bit more about customer

engagement, and hopefully hit home that we do need more funding and we do need model systems that other states can follow.

We try to publish all our lessons learned and to share as much as possible. But let me tell you. It feels like for every step forward, we are falling down two or three times, right, toward really good solutions.

So, next slide.

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ANDY ROHRWASSER: So, here is our horribly complex interoperability systems. We have multiple swim lanes. We have on top the birthing facilities and the health networks. We have in the second swim lane the health information exchange. In the third swim lane we have the newborn screening program and the infrastructure with kit management and LIMS. And then we have on the fourth swim lane, providers.

This is all complicated, so let me walk you through in one example.

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ANDY ROHRWASSER: Chain-of-custody environment. Historically, I did not know when a baby was born until the specimen showed up in the laboratory. In Utah, at least, vital, the birth certificate process is slow, and it's not really 100 percent available at the timing of the birth.

So, how can we generate, how can we think about generating a fool-proof chain of custody environment? Well, our approach to do that is to use the ADT method. So, admission, discharge, transfer message that is in place for every birthing facility. Than an order message in the middle lane, and then the physical arrival of the card.

So, in the first vertical, we have an ADT feed that notifies us when the baby is born. That triggers time zero. Then the next event is the receipt of an order message. So, now you can already see the delta allow us to interfere if this doesn't happen.

The third event is the card arrival

that triggers the initial completion of this chain of custody solution.

So, the next slide.

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ANDY ROHRWASSER: You can see that here. So, the short blue arrow to the left connecting the ADT message and the order message, that allows us to monitor whether a newborn screening was initiated. And it is also an indicator of timely connection.

The delta between the order message and the physical arrival of the card then will allow us to meaningful monitor the logistics process between the order and the physical arrival of the system.

So, with this high-level structure I can establish a 100 percent complete chain of custody environment.

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ANDY ROHRWASSER: So, this is the -- our first swim lane, right? So, we have again box

number 2, the ADT feed. We have a message component, box number, or circle number 3. Additional newborn screening information, and we have the electronic lab order and then the diagnosis and treatment option.

I want to talk a little about the light-orange circle, pre-birth information. If we would know at the time of the newborn screening collection that there are siblings that have CF or that they are MCADs, right, we would have all of a sudden accelerated interference of possibilities to make the system much better. So, we are also thinking about how to capture this information.

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ANDY ROHRWASSER: So, when we now think, we're shifting here a little bit as we want to explore the addition of significantly more disorders to our panel, we need a long-term follow-up solution.

Such a solution must be scalable. There must be a central system as well as a

distributed solution. The system must be automated. But again, in times of crisis, we also need the possibility to retrieve ad hoc and acute information.

Must be actionable, and unfortunately there are very limited models available to adopt today.

So, in the next slide --

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ANDY ROHRWASSER: In the next slide you see our conceptual foundation for that. It's again utilizing the ADT message, which is again universally available. So, how are we thinking of doing that?

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ANDY ROHRWASSER: So, the ADT message is our foundation for a long-term follow-up. So, we have on the left side, we have knowledge of disorder, of a newborn screening disorder that is established. Then what we can do, we can register that patient using a health information exchange,

right, or a master person index tool.

And then we can use specific information to now engage into ADT monitoring. So, in other words, if the infant is seen for a flu or for a broken arm, I don't care about it. If the infant is seen all of a sudden for seizures, in or out of network, we can establish queries to provide identity resolution. And then we can let the primary care or specialty care provider know that this is of importance.

So, next slide.

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ANDY ROHRWASSER: So, we were funded by HRSA to connect the Utah Newborn Screening Program with the Office of Vital Statistics. This was of course important for data cleaning, as the Florida colleagues reported, for record consolidation, and for the introduction of interoperating units' efficiency.

It's really a proof-of-concept study that shows feasibility. And we really use it,

right, to show, showcase that we can connect two different operating units.

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ANDY ROHRWASSER: So, again using our swim lanes, we reconnect the Utah newborn screening laboratory information management system. And the lower swim lane connects with the Utah Department of Health master person.

Next.

(Slide)

ANDY ROHRWASSER: And then this system connects with the Office of Vital Records for data cleaning. Again, let me say one more time: This has not been a huge solution, as the vital records information is in -- I don't know -- between maybe 20 to 25 percent of the cases not complete, and therefore of no utility for meaningful interference in a newborn screening process.

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ANDY ROHRWASSER: So, here is our process displayed graphically. So, the newborn screening LIMS connects with the Utah Department of Health Master Person Index, and that system is connected with vital records, with the CCHD system, or with the hearing screening program.

And establishing these connections will show us -- our plan is to show before-and-after information in terms of data quality, the reduction of FTE needs in this process, and to really update to have up-to-date records.

Yeah, and I think that was my last slide. Again, we are super-thankful. But we really want to plead with you to make more funding available and to also think about model systems and state systems that can use as global reference, right, for others to go and visit and ask question. How can we emulate something like this in our state?

Thank you very much.

NED CALONGE: Thank you, Andy. Thank you, Craig. Thank you, Juan.

COMMITTEE DISCUSSION

NED CALONGE: I know we're at time, and some people may need to drop off. But I would like to take the opportunity to see if there's any questions of our presenters. This was excellent information. I think it's a good demonstration of what resources HRSA can make available to states to kind of move newborn screening forward.

And, Andy, I assure you we heard the more-funding request as well.

Shawn.

SHAWN McCANDLESS: Thanks. I don't want to take too much time, so I'll be fairly quick.

One question for Juan is very specific about the Integrity system that you're using as an intermediary for the exchange. Is that like a third-party system? And is the data moving out to a third party and then back into the hospital or the Department of Health? Or is it an algorithm or a system on a state server?

And I'll just ask both of my questions now. The second question is for Andy or anyone else. And that is, how does this planning around interoperability -- how does it work with point-of-care testing? And is that included in the scope of the projects that you're working on to pull data directly from hospitals regarding point-of-care testing?

Thanks.

JUAN VASQUEZ: I'll go ahead and start if that's okay.

So, the Integrity platform, it is proprietary; however, in this case at the Florida Department of Health, it is on -- it's not a server at the department of health; it's cloud-based. But through the department of health infrastructure, so it does not leave the Florida Department of Health to a third party or to a different location.

It is cloud-based through the department of health. It's actually leveraging some of the advancements that were made after the

COVID response for ELR, electronic lab reporting for COVID tests. And so that infrastructure was able to change use cases or look at newborn screening as a use case, and then make some adjustments for also having the order end result going out.

But it is housed at the department of health using the department of health's cloud infrastructure.

SHAWN McCANDLESS: Thanks.

NED CALONGE: So, further questions? All right. Go ahead.

ANDY ROHRWASSER: I guess we have to answer Shawn's second question about the point-of-care testing, right?

The analogy, taking one step and falling two times, right, applies here. We are aiming to get the system, the broad system infrastructure up and working. And then of course we have to think about point-of-care testing, right, as it pertains to underlying necessities that might originate from newborn screening

disorders. But this is further down the road.

CRAIG NEWMAN: If I can just jump in there. Our standards that support point-of-care testing, but they rely on those hospitals pushing data and their vendors supporting that. And it's not well supported, to be honest.

One thing that we're looking at is new technology. You may have heard FHIR as the new interoperability standard called out by 21st Century Cures Act and various regulations. That actually would allow programs to go and ask for data.

It's not foolproof. You still have to know of the individual. You still have to have the authority and access. But it is a way to put things in the hands of the programs rather than in the hospitals. And to go ask for what you want rather than being a passive recipient.

So, a lot of promise there, but a lot of work to be done still.

NED CALONGE: Yeah. I appreciate your answers.

I wonder -- Susan. I hate to pick on you, but just wonder from the laboratory standpoint in your experience if you have any comments or questions on specific presentations, topics, and how you see this work moving laboratories forward?

Michele, I would include you in that.

Susan.

SUSAN TANKSLEY: Hi, thank you.

So, I just wanted to thank the presenters today. It is extremely challenging to get interoperability in newborn screening programs. And we in Texas have been working on this for years and years.

And so, I applaud any efforts and any information that can be shared broadly to enable other newborn screening programs to do the same.

I'm especially interested in the vital statistics matching. We have a process to do that now finally, but it's not -- it's a delayed process. So, it's more on the back end and not something where, you know, we can do the

flags and look for those matches -- or I should say mismatches, where you can see that you don't have a newborn screening specimen for a birth that's occurred.

So, I really look forward to seeing the data from that.

Thank you all so much.

NED CALONGE: Any other questions or comments?

Oh, Michele. Thank you.

MICHELE CAGGANA: I definitely would echo what Susan said. We've sort of worked on this for quite a long time. And it's really good to see the field moving and have funding available specifically for this issue, because it's a matter of not only getting the funding but then also figuring out how to percolate to the right people in your departments and convince them that this is a good thing for you.

And I think coming off of COVID, there's much more attention being paid to interoperability in other parts of health

departments in general. And so that I think it's a good time for newborn screening to try and sort of join that motion and be able to leverage what's been done for COVID and be able to apply that to newborns.

NED CALONGE: Thanks.

Well, I again want to thank Craig and Juan, Andy, first for your patience as we got through some business before you joined, and then just the really fantastic presentations that help us understand how the field is moving and provide a note of optimism to end on for the meeting for interoperability and how that can strengthen the newborn screening system, not just in your states, but as we learn from you in other states as well.

NEW BUSINESS

NED CALONGE: At this time I would ask if Committee members have any new business or announcements?

(No audible response)

NED CALONGE: I would ask if HRSA

staff have any announcements?

LETICIA MANNING: We do not. Just grateful to everyone.

ADJOURNMENT

NED CALONGE: I'm going to recognize that this was an emotional and challenging meeting.

And I hope that both the members of the public who may still be with us, our organizational reps, and our members hear my heartfelt thanks for the honesty and sometimes the courage that you all show in stepping forward to provide information, testimony, discussion, and really respectful diatribe as we try to make decisions that we feel are in the best interests of the babies born in our country and our public health approach to assuring they have the opportunity for the best health outcomes moving forward.

This is important work. The decisions are hard. The responsibility is heavy,

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.)