THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS

5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Friday, May 10, 2024

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P R O C E E D I N G S

Welcome, Roll Call, Opening Remarks, and Committee Business

NED CALONGE: Good morning. Welcome back to day two of the 2024 Meeting of the Advisory Committee of Heritable Disorders in Newborns and Children. I'm Ned Calonge, the Committee Chair. I am looking forward to another good day of discussions, presentations and information.

I'm going to turn things over to Leticia Manning, our Designated Federal Officer to do the roll call.

LETICIA MANNING: Thank you. Good morning, everyone. All right. I'm going to start with the roll call. From the Agency for Healthcare Research and Quality Kamila Mistry?

KAMILA MISTRY: Here.

LETICIA MANNING: Michele Caggana?

MICHELE CAGGANA: Here.

LETICIA MANNING: Ned Calonge?

NED CALONGE: I'm here.

LETICIA MANNING: Centers for Disease Control and Prevention, Carla Cuthbert?

CARLA CUTHBERT: I'm here.

LETICIA MANNING: Jannine Code?

JANNINE CODY: Here.

LETICIA MANNING: Christine Dorley? From the Food and Drug Administration, Paula Caposino?

PAULA CAPOSINO: Here.

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

JEFF BROSCO: 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 Institute of Health, Melissa Parisi?

MELISSA PARISI: Here.

LETICIA MANNING: And Chanika Phornphutkul?

CHANIKA PHORNPHUTKUL: Here.

LETICIA MANNING: And for our Organizational Representatives, from the American Academy of Family Physicians Robert Ostrander?

ROBERT OSTRANDER: Here.

LETICIA MANNING: From the American Academy of Pediatrics, Debra Freedenberg? From the American College of Medical Genetics, Cindy Powell?

CYNTHIA POWELL: Here.

LETICIA MANNING: From the American College of Obstetricians and Gynecologists, Mara Black?

MARA BLACK: Here.

LETICIA MANNING: From the Association of Public Health

Laboratories, Susan Tanksley?

SUSAN TANKSLEY: Here.

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

SCOTT SHONE: Here.

LETICIA MANNING: From the Association of Women's Health Obstetric and Neonatal Nurses, Shakira Henderson? From the Child Neurology, Society Margie Ream?

MARGIE REAM: Here.

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

NATASHA BONHOMME: Here.

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

SIOBHAN DOLAN: Here.

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, Sue Berry?

SUSAN BERRY: Here.

LETICIA MANNING: Great. Thank you. Okay. So now I'm just going to go over, as a reminder, the conflict of interest reminder. Please recuse yourselves from participation in any matters that will likely affect the financial interests of any organization with which you serve as an officer. If you have any

questions about anything that might feel like it's a conflict of interest, please let me know, or you can email me at lmanning@HRSA.gov.

And so I just want to remind folks about the meeting participation. According to FACA, all Committee meetings are open to the public. If you wish to participate in the discussion, there are procedures in the Federal Register. We did have public comments yesterday. We do have a couple of public comments today, and folks registered in advance to provide these public comments.

Only with the advanced approval of the Chair, or DFO, may public participants question Committee members or other presenters. And any public participation will be solely at the discretion of myself, as well as the Chair.

So, I'm just going to give a little overview of the webinar instructions again. Remember, if you are a Committee member, or Organizational Representative that's attending virtually, you can change your name. Be sure to include your first and last name, as well as your relevant organization, so that we can easily locate you if you would like to speak.

If you have any issues, technology type issues, please email Emma Kelly at ekelly@lrginc.com. And as a reminder when you are promoted to be a panelist, the system will briefly log you out of the meeting, and you will automatically rejoin within 10 seconds.

And now, I'm going to turn it back over to Ned.

NED CALONGE: Thanks Leticia. Again, I just want to

say how grateful we all are for folks who provided public comments yesterday, as well as our presenters. I thought the discussions were quite useful and continue to move the Committee ahead in our work, so thank you for yesterday.

We're going to first turn to the January 2024 meeting summary. I want to thank Committee members and the Organizations Representatives for reviewing the summary and providing edits.

The revised version was sent yesterday evening, and I want to know if there are any other additional corrections to the meeting summary before we vote to accept it? Seeing none, may I have a motion to approve the January 2024 meeting summary?

MICHELE CAGGANA: I move to approve the minutes.

NED CALONGE: Thanks.

JEFF BROSCO: I second.

NED CALONGE: Thank you, thank you. All right. Roll call vote please.

LETICIA MANNING: Okay. If you can just state accept or yes. So starting with Kamila Mistry?

KAMILA MISTRY: Yes.

LETICIA MANNING: Michele Caggana?

MICHELE CAGGANA: Yes.

LETICIA MANNING: Ned Calonge?

NED CALONGE: Yes.

LETICIA MANNING: Carla Cuthbert?

CARLA CUTHBERT: Yes.

LETICIA MANNING: Jannine Cody?

JANNINE CODY: Yes.

LETICIA MANNING: Christine Dorley?

CHRISTINE DORLEY: Accept.

LETICIA MANNING: Paula Caposino?

PAULA CAPOSINO: Yes.

LETICIA MANNING: Jeff Brosco?

JEFF BROSCO: Yes.

LETICIA MANNING: Jennifer Kwon?

JENNIFER KWON: Yes.

LETICIA MANNING: Ash Lal?

ASHUTOSH LAL: Yes.

LETICIA MANNING: Shawn McCandless?

SHAWN MCCANDLESS: Yes.

LETICIA MANNING: Melissa Parisi?

MELISSA PARISI: Yes.

CHR MANNING: And Chanika Phornphutkul?

DR PHORNPHUTKUL: Yes.

NED CALONGE: They're adopted, and as with all meeting minutes available on the website for people to review, so thank you. Kind of a roadmap for today. We're going to start the morning with a presentation on Qualitative Evidence Synthesis, which I'm quite excited about.

And we're going to have, as we heard, some additional public comments. After the public comments we're going to pick up the element we lost yesterday and talk about the nomination evidence review process for further discussion. We'll break for

lunch, and then have newborn screening updates from APHL.

So, we're a little bit ahead. Has Jane joined us yet, Dr. Noyes?

JANE NOYES: Yes, I'm definitely here.

NED CALONGE: Hi Jane.

JANE NOYES: Hello Ned, really good to see you.

Qualitative Evidence Synthesis: GRADE-CERQual Approach For Assessing the Confidence in Synthesized Findings

NED CALONGE: We invited Dr. Noyes to present some work that she's done in the United Kingdom. They're addressing similar challenges as incorporating qualitative research evidence into policy decisions. In particular, how do we synthesize qualitative studies into a coherent set of conclusions across a group of studies?

Jane Noyes is Professor of Health and Social Services Research and Child Health in the School of Health Services, Bangor University of the UK. She's a Methodologist, Systematic Reviewer, and Primary Researcher with a particular interest in complex health and social interventions.

She has a particular interest in developing methods for qualitative and mixed methods evidence synthesis, and the development and evaluation of complex interventions. Jane is regularly asked by leading global organizations to provide expertise and advice, particularly in the conduct of evidence synthesis and guideline development.

She contributes to the Wales Evidence Center and Public Health Collaborating Unit. She's the former Co-Chair, and now member of the Cochrane Methods Executive, a member of the Cochrane Editorial Board, Co-Founder and Lead Governor of the Cochrane Qualitative and Implementation Methods Group, Editor of the Journal of Advanced Nursing, and Editor of the new Cochrane Campbell Handbook on Qualitative Evidence Synthesis.

With that introduction, it's so much more than I ever knew, Jane. I'd like to turn things over to you.

JANE NOYES: Thank you. First, can I confirm--have you got the full screen or the presenter notes?

NED CALONGE: We have the presenter notes.

JANE NOYES: Okay. So I'm going to swap because you don't want to read those. So hopefully I've swapped this out of there.

NED CALONGE: Yes, perfect.

JANE NOYES: That's absolutely brilliant. So thank you so much for this invitation. I'm absolutely delighted to present to the Committee today. I'm absolutely thrilled that the Committee is interested in thinking about incorporating more diverse sources of evidence, such as qualitative research to inform decision making and recommendations.

I think congratulations to the Committee because you're ahead of the curve in this respect, and you could innovate guideline development in this area. Qualitative research can help with understanding the experience, the perceptions, the behaviors,

and the actions of people through spoken words, and through using vigorous methods to understand that behavior, et cetera.

This evidence can be collated and analyzed and used to inform decision making processes and is particularly valuable in understanding the various perspectives of those living with, or at risk of a heritable disease, as well as those people tasked with delivering services, treatments and interventions.

So, guidelines of traditionally relied on evidence to address a narrow set of questions, mainly evidence of the fact. That's all right to a certain point, but it means that guidelines are actually developed with a very narrow perspective. And congratulations to the panel for wanting to think outside the box, and to think how more broadly, how to include the perspectives of patients, their families and the public.

So qualitative evidence can inform key parts of the evidence to decision process. Qualitative evidence can help you with identifying the problem. Qualitative evidence can help you with the values and preferences of the various stakeholders, and issues such as equity, equity of access, acceptability and feasibility for all perspectives, and also implementation considerations in terms of interventions and strategies that you might make some decisions on.

I also think that qualitative evidence can actually help you from a patient and family perspective about the priority that it is to them, so families will have their own ideas about priorities, which might be slightly different to the scientific

literature.

Also, families and patients might actually be able to provide more information through qualitative entities about the benefits and harms of options, and also how much it costs them as patients, if interventions are implemented. So qualitative evidence has a range of uses to further enhance the guideline decision making processes.

There are rigorous methods to qualitative evidence synthesis, including qualitative question formulation, methods for searching, tools for assessing methodological limitations in primary studies, and a range of different methods of synthesis and reporting guidelines.

And I've put a picture up here, and a bit of a plug for my own book that's coming out, top left is the purple one, The Qualitative Evidence Synthesis Handbook for Cochrane Campbell. There are chapters already available on the website. On the right-hand side is the WHO Guideline for Handbook Development, that includes a qualitative chapter, and a miniseries on qualitative evidence methods.

So there's an increasing role for qualitative research in guideline development. Just to give you an indication of that between 2020 and 2022, 18 out of 29 WHO guidelines included qualitative research to guide decision making, and has made a real difference to decision making processes and WHO making them much more grounded in the perspective of various stakeholders, but very importantly, patients and the public.

So just to give you some examples of qualitative studies on heritable disorders, the first pictorial box at the top is a representation of a study which was entitled Returning Genetic Information about Risk for Alcohol Use Disorder to Adolescent: Findings from a Preliminary Qualitative Study of Precision Prevention. This particular study had a convenient sample of adolescents and adults.

There were qualitative interviews which explored attitudes about precision prevention of alcohol use disorder for youth, they undertook a thematic analysis to explore acceptability, potential harms and benefits of a precision prevention model for youth. You can see in the middle of the interview, themes in the little box, there are some potential benefits and potential harms.

All of that information would have been vital to feed into a decision-making process of a panel such as yours, especially thinking about implementation. So it would have been very important evidence to have if you were thinking of implementing this particular intervention.

The box below is a slightly different type of study. This is a qualitative study, what do families affected by Turner's Syndrome think of a variant tissue freezing in childhood. Again, semi-structured interviews with those family members affected, to get their ideas of what they would want if there was going to be a recommendation.

And again, this information will be vital to go into a

decision-making process. These studies were published in the academic literature in journals, but that's not the only place that you can find qualitative studies. We call the third sector of organizations in the UK, I guess you probably call them NGOs, or patient support organizations.

I see from your roll call that's you've got many patient support organizations with you, which is fantastic, but these organizations can also conduct their own research. This is sort of a study that came from the Genetic Alliance in the UK, which was conducted with people with unique and rare conditions to get a better idea from their perspective, as to how their care could be better coordinated, and how their experience of services could be further improved.

Again, this is pictorially presented here, but there was a large report behind it, which could be synthesized and used to inform guideline development. It's also possible to conduct mixed method reviews, and this is one example here that I've put in, which is Parent-Child Communication and Reproductive Considerations in Families with Genetic Cancer Predisposition Syndromes.

This review contains qualitative, quantitative and mixed methods studies. So that provides you with sort of a bit of background context of the types of evidence that is out there. I'm going to focus on qualitative evidence now. I'm moving on to the new approach, GRADE CERQual for assessing the confidence in synthesized qualitative findings.

So why did we develop this approach? Well, we developed GRADE CERQual as part of a qualitative evidence synthesis that was commissioned for World Health Organization guideline, and it was the first time that the WHO panel had seen qualitative evidence integrated in the guideline panel process, and they were very familiar with GRADE.

So, we decided to develop a system that was very similar to GRADE for quantitative evidence, so the guideline panel would recognize it, and it starts from the similar sort of stable, but would actually give the guideline panel more members, a representation of sort of a level of confidence in the synthesized qualitative findings.

It’s broadly similar to the domains map on to GRADE with the exception of dissemination bias. We’re doing a program of research on dissemination bias and qualitative research to see if we need to develop an extra component, and we’ll keep you informed of that.

So what happened at the panel meeting? Well, the panel members really liked GRADE CERQual, they liked having an assessment of confidence in the synthesized qualitative findings. It helped them in their decision making. It’s certainly meant that a broader representation of patients and public opinions, and representation of their experience was put to the panel, and it also meant the panel members refrained with chipping in with their own anecdotal experiences and trying to actually superimpose their own opinions on the decision-making process, so it's very much

more of an evidence informed process. So, CERQual is applied to individual synthesized findings, and there's a technical term coming up, which I'll explain in lay terms in the next slide. But what is qualitative evidence synthesis finding--technically it's an analytical output that describes the phenomenon, or an aspect of the phenomenon.

And the qualitative researchers amongst you will understand that. What that means in practice is that findings from qualitative evidence syntheses can be presented as themes, as categories, as theories, they can be both descriptive, or more interpretative, and I'm going to show an example next, as to what a finding looks like for those of you who are still trying to still put all of this together.

So, this is the end product once CERQual has been applied, and it's produced, you've produced a summary of qualitative findings tables. So this is taken from a qualitative evidence synthesis that was undertaken to determine the barriers and facilitators to the implementation of lay health worker programs for maternal and child health, so nothing to do with hereditary disorders, but just an example here to show you.

If you track down on the left-hand side of the box, you'll find a heading with a review finding, and there's a statement here. It's a summarized review finding, and it says while regular salaries were not part of many programs, or other monetary or non-monetary incentives, including payment to cover out of pocket expenses, and work tools, such as bicycles, uniforms

or identity badges were greatly appreciated by lay health workers.

So that was the summarized finding from the synthesis. Moving along, you'll see that there was an overall CERQual assessment of confidence, which was considered to be moderate, and then moving across more towards the right, there's an explanation of the CERQual assessment. This finding was graded as moderate confidence because of minor concerns regarding methodological limitations, relevance, adherence and adequacy.

And then on the right-hand side of the box you can see the studies contributing to the review finding are listed, so everything is transparent in order to bolster the transparent process. So, I'm going to move on now to show you how a GRADE CERQual assessment is undertaken.

For those of you that are new to GRADE CERQual and qualitative research, I'm going to do it in an easy-to-understand pictorial way, so I'm going to represent this graphically, so it's much easier to conceptualize. For the qualitative researchers amongst you this will all be, you know, a piece of cake, so please bear with us and let's hope that we can get everybody on the same page.

So here is the scenario. Decision makers are considering a new healthcare service, but before they introduce it they want to know whether those affected, including patients and healthcare workers are likely to accept it. Our review of qualitative research is commissioned and conducted, and one of the

findings describes women's experiences of intervention.

And the question is how much confidence should we decide to place in that finding? So let's go through each of the CERQual components. So then to start off, you're going to see some pictures emerging into the frame, and each picture represents a study and a perspective.

Now, ideally what you want is a range of high-quality studies that represent different perspectives that map on to your review question. And you can see here I'm putting studies that are represented by pictures into the frame. There's a range of different perspectives and I've listed here, which is ideally what you want.

You want lots of theoretically sampled perspectives that represent all the people that have had intervention but mirrors the population that have received intervention as a whole. That's the ideal, but quite often the reality is very different, you know, there are a number of things that you needed to take into consideration. We're going to go through those one by one.

The first thing, I'm going to take some studies away, now some pictures away. The first thing is that you often get poorly conducted studies, so I am replacing some of the well conducted paintings with some less conducted paintings. You could see that these are methodologically much weaker.

We have tools to assess the methodological limitations in primary qualitative studies. You assess all the studies contributing to synthesized finding, and you would actually come

up with an overall assessment of concerns at each study level to start with, and then of the collective studies that contribute to a review finding.

And that's called an assessment of methodological limitations. It's very similar to the risk of bias assessment if you're using GRADE. So let's take away those studies that are weak methodologically, and let's move on to the next component. I'm going to look at relevance next, and indirect relevance.

You may well find that some of the studies ask the same questions, they're interested in women's experiences. But the studies themselves maybe actually conducted with men or healthcare workers, who have given their own experiences of what the women's experiences are, so they're indirect accounts of the women's experiences.

That's not as good as asking the women themselves, but if you're in a situation where you haven't got enough studies, well then you have the direct evidence from the women. And sometimes it's helpful to have a proxy perspective, but not always. But ideally you would like direct evidence, but you don't always get it.

So it is a concern if the studies aren't directly relevant to your question. They don't actually explore the women's perspectives themselves. So, let's take the men and the healthcare workers away, and have another type of relevance, partial relevance. I'm going to add some more pictures now. You may well find that some of the stuff is only relevant to part of

the question that you're interested in, and they don't represent the women, the sort of global women around the world from some settings.

And this is actually represented as partial relevance. You can see, I did some pictures with what like very well to do women, but don’t globally represent the women in more settings. It's still okay to include them, but you would actually need to think about what concerns that might actually raise when you're doing your overall CERQual assessment, so that's partial relevance.

I'm going to move on now to coherence. So a third issue is the fit between the underlying data and the finding itself, and we refer to that as coherence. In some findings they may be more or less a better fit with the data that supports those findings. And you can that I've superimposed here a small picture, which looks very much like the studies, of the pictures underlying it, so this is a very coherent picture.

And you could say that you wouldn't have concerns about coherence here. But sometimes that isn't the case, that the finding doesn't represent the coherent picture. And you may well find that you could actually isolate parts of the data, so I'm going to put up a smaller picture now. This is a finding with a smaller subset of studies or paintings that represent a smaller finding, a smaller context.

This might be simpler and clearer but might not be so coherent as it doesn't represent all the data underlying it. So

this can be a particular problem. It may not be, but it could be, it depends on the context. But coherence might be an issue you want to think about.

The last case with coherence is if you're developing a more interpretative finding that points to developing new patterns or new theories, which is quite common in qualitative evidence synthesis, that once you assemble the studies together, you begin to see new patterns and new meanings that weren't actually there in the original study, so you can come up with new interpretations, that are more abstract or theoretical.

And you can see here that I've superimposed a smaller picture with a more abstract interpretation of the underlying data. And that could flag some possible concerns about coherence that you'd need to think about. So I'm going to take that away now.

The last issue is adequacy, and I'm going to take some studies away, and the fewer studies that you have you begin to worry about adequacy. You need a specific, you know, a certain amount of data, adequate data, to support the finding. That's the first element that you would need to consider. The second element around adequacy is the richness of the data, and I'm returning some pictures to the frame that aren't rich. They're in grayscale, they don't give a particularly good or deep understanding.

It's very difficult to make out what the picture is actually telling you. So these data is not sufficiently rich to

explore and understand the pattern that's emerging that would develop into a finding, and this would actually cause you some concerns.

Okay. So for each CERQual component, you would need to identify your concerns, and whether these are no or very minor concerns, or an understanding that no qualitative study is perfect, so you need to take sort of a pragmatic approach here. So there might be no, or very minor concerns, minor concerns, moderate concerns or serious concerns.

And then you take those assessments to each of the components to come up with a combined assessment, an overall assessment that combines the four components together, and that's the assessment of competence. And you can have high confidence, moderate confidence, low confidence, or very low confidence.

And that's what feeds into the table that we looked at just now, and this is the table that would go to the guideline development or the guideline development committee, the panel, and this is the type which will actually feed in, in a transparent way to help with decision making.

So finally, if you want to learn more about GRADE CERQual, there are papers published in the academic literature. We have a website, and we do quite regular trainings, and I would be delighted if you were more interested and wanted to learn more.

So I'm going to stop sharing my slide presentation now, so we can open up to some questions.

Committee Discussion

NED CALONGE: Thanks very much, Dr. Noyes. We're going to open up for questions here, and our process is, just so you know, is that we have our panel members asking questions first, and then Organizational Representatives, as we deplete the questions from the panel.

So, the first question I see comes from Jennifer Kwon.

JENNIFER KWON: Thank you so much for this informative talk. The newborn screening program that we're considering now for inclusion for U.S. wide newborn screening is for Duchenne Muscular Dystrophy, and one of the things that hasn't appeared in the evidence review is the fact that Duchenne Muscular Dystrophy has been screened in newborns in many different parts of the world since the 1970's.

And in many of those regions there has been some qualitative research to sort of explore family responses, and then I just also think so there's that piece. But of course, it's in a different time with different treatment options. And then there's just the fact that there are probably, there may be articles about why the program's stopped running.

So I think for example in Wales, that was one of the more recent long-running programs that stopped running after a couple of decades, and there were some articles written about that. If you were considering Duchenne Muscular Dystrophy as a

new newborn screening enterprise, how might you look at those past papers, and those past qualitative studies to maybe inform current decision making? I know that's a pretty broad question, but I was curious about your take on it.

JANE NOYES: Yeah. Those are excellent questions. And I actually live in Wales, so that program is very familiar to me, so where you start with a qualitative evidence synthesis, and how you shape out your question is fundamental. I think the historical context can be really important, depending on your question.

But also, so is contemporary practice, so it's the decisions that you have to make when you're actually shaping out the questions. So I focused today on GRADE CERQual, but I could equally have done a whole presentation on developing answerable questions, working with key stakeholders to articulate what their priorities are, and what might be important.

And the first stage of that is always doing your scoping searches to see what evidence is out there. And you know, going from that. So, I would say both would be really important. If you've got the time and energy to do it. Both would give you different perspectives, and both would actually probably feed into your decision-making process.

If I was to push what would be the priority, the contemporary practice, and starting with the most recent evidence first, I think probably is the best bet to start, or if there is a seminal policy change, and you want to work forwards or backwards

from that, that might be helpful as well.

Going too far back I think is problematic, because you know, policies and practice changes too much, and people's experiences 20-30 years ago probably wouldn't be contemporary to now but might give you a flavor of some of the issues that they faced, and whether they changed or not.

NED CALONGE: Other questions? Jane? Sorry, go ahead.

KAMILA MISTRY: This is Kamila. I have a question. Thank you for a wonderful presentation. I had a quick question. You know, when we were looking at qualitative and quantitative together, kind of side by side, we tend to look at them in silos. And I think when we're trying to make decisions it's almost as though, you know, this Committee and others, you know, sort of thinking about both types of information, we need to be able to-- I mean our minds tend to want to weigh them.

And I don't know, you know, I think I loved the last slide where you actually showed us, you know, the type of information that the Committee would get, or someone would get, in terms of trying to understand I was going to say strength of the evidence, that's more of a quantitative way of saying it. But in any case, how do you think about that in the work that you're doing?

There's always, I feel like the gold standard is always the quantitative in some ways in our mind, and how do we work away from that? And as a Committee really try to understand the distinct, maybe advantages or strengths that we're going to get

from qualitative that we might not get from the quantitative.

And so, maybe that would help us to think about them together. Anyway, I'm sure, Dr. Noyes, you've thought about this a great deal. That would be really valuable for us to understand.

JANE NOYES: Sure. And again, I could have done a whole presentation on this. So in Cochrane, we have developed methods to integrating quantitative and qualitative and data juxtaposing it, putting it into matrixes. The sorts of things that you can do with that, you can identify where sort of the outcomes of targeted interventions of the outcomes, the patients and their family members want, or feel that are most important.

You can think about the components of interventions, and whether they're actually targeting the behaviors of people, et cetera. So that's one thing. You can do an integration of the qualitative and the quantitative. And we do that quite a lot. If there's a quantitative intervention, a fact review, we will do a qualitative evidence synthesis to supplement it, and then do a data integration of the two syntheses.

The second thing is that in most guideline panels there's an evidence to decision framework. I commonly work with the DECIDE framework, which is part of the GRADE suite of tools. WHO have their own evidence to decision frameworks. At most those actually serve as frameworks to integrate the evidence in a coherent way to present to the guideline panel.

And I do think that, you know, the guideline panel members do need some training on how to look at the qualitative

evidence, to determine what it's saying, how it might be useful, how it might be usefully used.

And I think that, you know, the WHO panels for example, are very experienced using qualitative evidence, and they can see the value and the benefits of actually integrating it into the decision-making process without getting caught up in, you know, it's not an effect size, so it doesn't actually mean anything.

So qualitative evidence can be very meaningful to panel members, very helpful. It has to be presented in a certain way that they understand it, can make sense of it, and make a decision from it, and I think that's the key thing.

KAMILA MISTRY: Thank you.

NED CALONGE: Jeff?

JEFF BROSCO: Jeff Brosco. It's great to see you again Jane, after our conversation a month or so ago. The sort of questions that often come up for this Committee that are particularly relevant is if a family gets information that they weren't necessarily looking for in the first place because it happened out of a newborn screening program, you know, is that good or bad?

Because some families worry a lot, and some families love having information. And what we've done over the last year is we started with some presentations from Aaron Goldenberg and others about the kind of qualitative research that's going on, funded through NIH and others, and then we had Beth Tarini and Sara Ackerman talking about somewhere qualitative research is

already, kind of an up to date of the kinds of things that matter.

And now you are coming to help us say how do we synthesize this to make sense of it? And I guess my question for you is can you think of an example of in your work where decisions by panels were changed, or how it influences? Are there specific ways that you can see how this was applied and made a difference in a policy that came out?

JANE NOYES: Sure. I haven't got experience with heritable diseases, but I'd probably make two points here that qualitative evidence synthesis, and qualitative research in general is about eliciting people's values, perspectives, experiences, et cetera, and how they make sense of it.

So people come from different backgrounds in all shapes and sizes, so they're not going to make sense of it in the same way. And people make very different decisions based on, you know, where they're coming from with it, and I mean we've all seen very healthy women, for example, with a normal pregnancy deciding to have an elective Cesarian section when it's not clinically indicated.

So understanding why they make those decisions, and you know, potentially put themselves at risk of a surgical procedure is really, really important. So you won't get one answer out of this, you know, there are multiple truths going on here, and some people will have, you know, different reactions to different scenarios in the families, or you know, different information that they're given.

So I think you have to accept that to start with, that there will be a range of perspectives. Have I seen where qualitative evidence makes a difference at the guideline panel? Sure. I mean, you know, I'm sure Ned can fill you in about the work that we did on disaster preparedness and response, which is a long way from where you are.

But nonetheless, the qualitative evidence, syntheses, and the qualitative evidence did make a difference to decision making. Probably nearer to home, I did a lot of work with WHO about risk communication, which is probably nearer to you because you have to communicate risks to families.

And we looked at where there wasn't evidence of the fact, because there's a lot of scenarios that you might look at.

There isn't good evidence of the facts. You might have to rely on the qualitative evidence, and we developed a whole guideline on risk communication without much evidence of the facts, but with qualitative evidence of what people wanted, and what they felt you know, what people felt they actually responded best to.

So I'd say the WHO risk communication guideline was the best example of that, but all the guideline panels I've been involved in, the qualitative evidence has made a big decision to the decision making, or made a big impact on the decision making, especially for, you know, feeding in patient and public values and preferences.

Whether interventions are acceptable or feasible, and

there's the intervention side of it, big considerations have come through the qualitative evidence.

JEFF BROSCO: Thank you.

NED CALONGE: Jennifer, before--this is kind of related. Jane, so one of the issues I think we face on the Committee is an imbalance in the voice, so we have a rich, I would say you would call it a thick research face from families and parents who have experienced the condition within their family and have come forward as advocates for screening.

And so we hear, we have a lot of evidence on that side, and we have very little voice from people who were screened positive, and chose not to come forward, or not to have their child, or somehow made different decisions. Or didn't appreciate having that information, or some might have negatively reacted, which I've seen on an individual basis to suddenly finding out that their child was--their infant was tested for a condition that they never said I want my child tested for.

So there's a lot of information on one side of the qualitative, and there's very little on the other. And I wondered how that kind of comes out in qualitative evidence, and how you deal with that imbalance.

JANE NOYES: So I think the two purposes for doing a qualitative evidence synthesis, one is to synthesize what's there. The second is to identify the gaps, and to develop a research agenda and put it out there in the public domain. Our researchers are pretty good at picking up the research agendas, and the

funders are pretty good at funding the research so that you can ultimately fill the gaps in what's known.

In addition to having an academic team, a review team, we do a lot of patient and public consultation, and we do do a lot of coproductions in our review. So if we do have big gaps, we do go out and, you know, do a lot of engagement with consumer groups, the patient groups, the support groups to see if we could actually fill in some of the evidence.

But we're very clear as to what is empirical evidence coming through published studies on what is sort of, you know, the more co-produced thoughts and opinions who are actually advising us. So there are two ways of doing it. Identify the gaps to put the research agenda out, try and plug the gaps with good patients and public involvement and wider stakeholder engagement.

NED CALONGE: Yeah. I appreciate that. The two studies that Jeff mentioned are actually looking at trying to address the gap and provide more information, but there will still be an imbalance I feel, but at least we'll know more, so I appreciate it. Jennifer?

JENNIFER KWON: So Ned, actually my question was similar to yours, but I'm going to be even more concrete, and the problem that I think I personally have with qualitative research is there are people who participate in studies, and there are people who don't. And in many ways the people who have had negative experiences, or whose experience with let's say early, presymptomatic diagnosis, which is you know, a form of experience

that can inform newborn screening obviously, may have taken an unusual path.

And you want to try to collect that. So just as an example, going back to Duchenne, I have families that I care for, and for a variety of reasons they knew that their son had Duchenne at the time they were born. They asked to find out and they knew. And did this result in them taking advantage of clinical trials, or newer treatments? No. It did not.

And so, those families are also, you know, when I sort of gently probed about the fact that newborn screening is, you know, here, and/or is being presented, and would they like to share their experience, they're pretty clear that they don't want to share their experience.

And so, the way that I'm trying to sort of look at these issues, look at some of these barriers is that my particular interest is if we have more children identified presymptomatically with a disorder that really extends through their lifetime. And not only does it extend through their lifetime, but every two years there's some pretty big change in management. How do I best prepare families for this in this country where we do not have universal healthcare?

Where the treatment and care of children is very different than the treatment and care of adults, and so to try to put all those components together I have actually, I'm working with a qualitative researcher to interview young adults and their caregivers about their past experience and barriers, and you know,

what they're looking forward to in the future.

And because I come from a state where I happen to live in the state capitol, I'm hoping to use this as a steppingstone to present my findings, to try to change some practices in the state. And so the qualitative researcher, we were talking about it, and I was shocked to find that she thought that 10 people would be like quite a lot of people to have in a study that I was thinking about.

And I was just sort of curious if, and I think that's part of the problem maybe that people who are more quantitative have with qualitative research is that the number seems small, and it seems likely that they, you know, how do you get at sort of the rich diversity of opinion with that small of a number, so yeah, so I'll let you chew on that. Thanks.

JANE NOYES: Yeah, there's a lot in there to unpack, so I also am a qualitative researcher, and I also run trials, so I can quite easily move between the two. So, a properly designed qualitative research is unique to the context and the question that you're trying to answer, so if you have a large population with lots of different opinions, you need a large sample that represents that population.

We call that a theoretical sample or a purposive sample, and you prespecify that, and you actually articulate all the types of characteristics in the sample that you want to recruit to, and then the sort of potential numbers, and then you think about things like data saturation, so you stop recruiting

when you're not getting any more data, but you've covered all the different perspectives that you think are important, to address your question.

The other thing is that, and I find it easier to do research if I'm independent of the clinical team. If you're a clinician that's actually managing children there's a power play there, and the power relations in qualitative research are really, really important.

You know, I think some of the best qualitative research sometimes comes out of the government organizations or the parent support groups because the power plays there are completely different. It's a different environment. So we often recruit via patient support groups, for example. And I'm not seen as a clinician. I go in completely as just a qualitative researcher who works independently, very independently of the clinical team.

And you get more people that are willing to talk to you because I think sometimes, they find it awkward if they're talking or knowing that the data is being collected by their clinical team, and then there is a sense that you know, that it can be affected by it et cetera.

So I think there's all sorts of issues around power and interplay between people, how comfortable people are, and to be recorded, because of course we record the conversations. It's all done in a very rigorous way. So there are lots of different things that you can do to conduct rigorous qualitative studies. And like all studies, we have difficulty with recruitment.

You do to trials, you do to qualitative studies, but there are ways that you can engage with through the communities to find, you know, people who represent the different perspectives and can tell their stories, and then we can look for the various patterns.

So, I don't know that that answers your question or not. I can appreciate as a clinician how frustrating it is when you want to know, but find it quite difficult, and then you have a qualitative researcher who doesn't quite conceptualize that you're going to have to do quite a big study to make it rigorous.

JENNIFER KWON: And just to reassure you, I think that for, I mean the Duchenne population in the state that I live in is somewhat finite, and so I think that we may find saturation with the number that she has suggested, and I also think that we have sort of integrated that separation as you say.

Like even though I'm very keen on having this study done and getting the funding for it, she was also very keen about that keeping her research separate from identification with the clinical work but thank you so much.

JANE NOYES: Pleasure.

NED CALONGE: Jane, this is Ned again. One of the challenges I remember from the emergency preparedness study was finding a group in the U.S. that knew how to do qualitative data synthesis. So, there are lots of people who are really good qualitative researchers, but the concept of synthesis across studies is at least in my institution, and as I look around, it's

still something that is an emerging innovation.

And I notice your book doesn't come out until 2025. So, I just wonder if you see an increase in the number of institutions and groups that have some experience with qualitative data synthesis that are undecided upon, we could reach out to, we could consider their skillsets and how they could benefit the Committee if that was something we wanted to move towards.

Not that we wouldn't want to bring you over. We would be delighted. But I was just wondering if we're getting better at this.

JANE NOYES: Well, the answer to that is yes, and to reassure you, there are quite a few chapters up on the website already of the book, but the whole thing won't be out until next year. So, I've worked very closely with AHRQ, they asked me to do a lot of training with them. You would all be familiar with that organization.

And we did I think it was five or six demonstration projects where they added a qualitative evidence synthesis to their usual guideline development work. And they did brilliantly, and they got the reviews published, and I'm currently working with some of them to do subsequent qualitative evidence syntheses.

So they know our building capacity and capability in their area. There is a series of webinars on the Cochrane website for example, you know, great training resources and introductory modules. But of course, you know Cochrane groups or Campbell groups are very active in North America, so if there is a lot of

experience out there.

I just think it's a question of you need a few groups to get going on this brilliant training out there. In the UK now in Europe, you know, with guideline development it's so usual now, and we've got a critical mass of qualitive evidence synthesis that it's unusual to not have a, you know, sort of qualitative evidence feeding into a guideline if the question is appropriate to be answered by qualitative evidence.

So, it's just a question of people getting on and doing it, getting some demonstration pilots. You might want to think of a pilot guideline that you'd want to do some pilot qualitative evidence syntheses, so somebody like me could support you through it, you know, to test out the value of it to your Committee.

You know, choose a sensible question where there's some good qualitative research there, and do it as a demonstration, and see how people feel about it.

NED CALONGE: Thanks. Kamila?

KAMILA MISTRY: Thank. So I am from AHRQ, so the Agency for Healthcare Research and Quality, and I know you've worked with Sue Chi and other people from the Evidence-Based Practice Center (EPC), so I do want to make sure folks know that that is something that we've been doing for quite a while. And as part of the infrastructure we have in the Evidence-Based Practice Center, we focus a lot, obviously, on quantitative findings, and really thinking about synthesis.

But we are also integrating qualitative findings, and

it really so far has been really linked to, you know, the question that we're answering, and the evidence, and how we're looking at it. And so I think we're moving closer and getting more comfortable, I think as Dr. Noyes said, in terms of how we're doing our work and what we're doing.

But I would, you know, very much encourage, sort of, we could certainly connect with the folks there, and I know that we're sort deepening our expertise in that area. But one question I think that I keep coming back to is the one I mentioned at the beginning, which is sort of at--we recently did a review of respect for maternity care, and so we were looking at qualitative and quantitative.

And I sort of felt that you know, we were getting our peer reviews back from folks. We do the EPC report, and then we send it out for peer review, but there's still maybe a bias in terms of the way that we're thinking about quantitative versus qualitative. And so, I think there's still some work to be done in thinking about that overall synthesis or thinking about how do we think of both of these kind of side by side, or in terms of you know, informing decision making and work moving forward.

I'm not sure we're quite there yet, but I continue to see that sort of coming up as an issue, and you did speak to that, but so I welcome a discussion between, we can actually bring over folks from AHRQ to talk about this more deeply too, so thank you.

NED CALONGE: One of the quotes from Dr. Noyes that I carry around with me all the time is that you have to recognize

that quantitative and qualitative research answers different questions, and so you shouldn't actually apply qualitative research to questions that need a quantitative approach. And the opposite is true.

So it's an issue about in my mind less of weighing, which is more important, but using the synthesis in the proper way in the decision making framework.

KAMILA MISTRY: Yeah, I think that what I'm saying is that I think our brains because of the way that we're trained, or maybe biased, it tends to go to wanting to weigh. And I think it takes a very concerted effort to understanding the distinctions, and you know, maybe the strengths in both. And trying to make sure you don't do that, so I think it's important because it continues to come up, you know, in the work that we're doing across the board regardless of what we're studying in terms of the work of the EPC.

NED CALONGE: Yeah. I couldn't agree more Kamila. I will admit to everyone I find comfort in numbers, so yes. Just the way my mind thinks, yeah.

PAULA CAPOSINO: I just have a question about, oh I'm sorry, Paula Caposino with the Food and Drug Administration. When you were putting up the pictures, and you were talking about the proxies, I always wonder, you know, here with this type of research, or this type of information, you know, everybody is a proxy because you actually don't understand the perspective of the children at all.

And it's an impossible question. I'm just wondering how you think about that when you don't, you know, when everything is pretty much a proxy, you know, including every perspective.

JANE NOYES: Sure. That's a great question, and my background is child health, so I'm very used to interviewing children from a very young age to get their perspectives as well. We've done lots of qualitative studies with children, and young people. Of course, you know, there's obviously a developmental aspect. There's a certain point when you can interview a child and get some, you know, some meaningful data from them.

And you know, and older children can still retrospectively look back and reflect on whether the right decisions were made for them, and we should rightfully include them. The U.N. Convention on the Rights of the Child says that children should be involved in all decisions that involve them, and so you know, we have a moral implication imperative to include children's voices.

But you are right there are very few qualitative studies, and you know, a lot of the ethics committees are trying to protect children from research, we are having quite a revolution in the UK and Europe at the moment by saying that we're harming children more by not including them in the research studies, than we are by excluding them to try to protect them.

So you know, maybe if we could follow that approach we'd get better data and more inclusion from children into these studies.

NED CALONGE: Yeah. Your last comment is interesting because I think the National Academy just published a report on including pregnant women and lactating women in research, and I think came to the same conclusion that we're actually doing more harm by not including women and pregnant persons in randomized control trials, and lactating people as well.

So, I think we're going to see changes. I haven't seen that report for children yet, so we need your results over here. Any other questions? Yeah, last question Robert.

ROBERT OSTRANDER: Sure, thanks. Robert Ostrander, American Academy of Family Physicians. Thank you for a great talk. In my world this is going to have lots of implications outside of this Committee. I am struck by what I think you've accomplished today with the group in that it will allow us to think about the validity and quality and competence level of the qualitative things we've been using right along.

We haven't called them qualitative studies, but we have spent a lot of time--still not loud enough, okay. Have spent a lot of time in public comment sessions hearing from folks, and you know, and Ned pointed out, excuse me the limitations of that. And we've also spent a lot of time hearing individual anecdotes from organizational reps and Committee members about their impressions.

And I think we have taken, the Committee has taken all of that into account, but now we can say how confident are we in that information will help us even right now before we have other studies, and I appreciate that. So what are your thoughts, or

should we--things that really aren't methodologically sound at all, should we consider those other than as human beings?

JANE NOYES: So, sometimes in the decision-making process you don't have the rigorous evidence that you need, and sometimes some decision is better than no decision. And in the meantime, you could put out your research agenda to try and actually plug those evidence gaps.

The anecdotal evidence from the groups, what we call the patient to public engagement where I live and work, is equally as important, but more as a triangulation of the research findings that have been very carefully and rigorously, hopefully, put together and theorized and designed. And we've got the ability to differentiate the well conducted studies from the last well conducted studies.

So you know, exactly the same domain as the trials. We can differentiate the better quality trials, and the less quality trials, and we can look up that impact. We could do sensitivity analysis by taking weak and strong qualitative studies in and out, so we can do lots of things.

Or we can triangulate our qualitative evidence synthesis findings with patients and public perspectives to see if they hold true, so there's lots of things that we can do to come up with a sort of an evidence trial to decision making.

NED CALONGE: Well, Dr. Noyes, thanks so much for your time today. It's been great, delightful to see you again. We look forward to thinking more about our engagement with

qualitative data synthesis to inform the Committee in our decision making, and you've moved us forward a lot. Thanks so much.

JANE NOYES: Thank you. It's been my pleasure, and I think we'll make a qualitative research of you yet, and we're slowly moving you along a journey towards qualitative evidence, it's been my pleasure. Thank you so much and enjoy the rest of your day.

NED CALONGE: Thank you.

(Applause.)

Public Comments

NED CALONGE: I'd like to move on to our second public comment period. And just pause for a moment to take a breath, and then I'd like to welcome Maria Kefalas up for the first public comment.

MARIA KEFALAS: My name is Maria Kefalas, and I am the Executive Director of Cure MLD. As a parent advocate since 2013, I'm here to state that MLD has met the requirements for inclusion in RUSP, an effective assay, an FDA approved gene therapy, and a standard of care that has been successfully implemented in the EU and UK.

LENMELDY is widely viewed to be one of the safest, most durable and transformative gene therapies in the world. The oldest U.S. patient received gene therapy in the original Italian trial back in 2009, just before his first birthday. Giavanni is

now 15 years old, six feet tall, his friends and classmates have no idea he has MLD.

When Giovanni provided his testimony to the FDA he stated, "I guess gene therapy works because I should be dead." MLD is a devastating disorder that causes tremendous suffering for the child, and taxes the healthcare system. According to my late daughter's physicians at the Children's Hospital of Philadelphia, Cal had 1,712 confirmed provider contacts over a ten year span.

194 blood tests, 42 x-rays, 22 ER visits, 16 admissions, including three to the PICU, which included one intubation, 11 ultrasounds and two MRIs. I entreat the ACHDNC to move as quickly as possible to include MLD on the RUSP. Of the dozens of condolences I received after Cal died, a message from Dr. Michael Gelb, the scientist who invested the Newborn Screening assay for MLD, rises above the rest.

His message was simply I am so sorry we could not save Cal. It is too late for my daughter, and so many others, and it is in your power to give our children a different ending to their stories. It is intolerable to tell newly diagnosed families that I meet today that we have an FDA approved therapy, but we can't use it for your child because there is no newborn screening.

I urge the Committee to act quickly. Thank you for your time and consideration.

NED CALONGE: Thank you. Next, Dean Suhr.

DEAN SUHR: Good morning. My name is Dean Suhr. I am Founder, CoFounder and President of MLD Foundation. We're a

23-year-old advocacy organization focused on caring for families and children with Metachromatic Leukodystrophy. I think this is my 14th or 15th year of traveling to these meetings.

I so appreciate the work that you all do, and the challenges that you face. I'm going to edit my comments, so excuse a little roughness, because I think Maria has covered some of where we're at. We first came across the gene therapy in 2005. Two researchers at a conference here in Washington, D.C. with about three dozen other researchers around a table.

And everybody scoffed at the idea that gene therapy could work at all, much less in children. And we stuck with it. We participated in clinical trials, we actually escorted some families over those trials, and as Maria has reported from one family, there are many, many families that are experiencing similar results. It's important to note that not only are these children living normal lives, but they are growing up.

They're teenagers at best now because most of them were infants when they were transplanted, or younger children. But they are going to live normal lives. They're going to contribute to society academically, socially and financially, and perhaps equally as important is that their families, their parents, it's Mother's Day weekend, Happy Mother's Day to all, they'll know their parents as mom and dad, not as caregivers.

And society will know them as contributing workers that are contributing into social services as opposed to being beneficiaries. So I know your purview is very focused on value

and benefit and often you all talk about whether that benefit accrues to the child or the family and/or society. The gene therapy, LENMELDY, here in the U.S. is creating a new generation of MLD children and families that show extraordinary value.

The therapy also has shown extraordinary values through ICER and NICE in the UK reviews, so don't be shocked. I'm sure you've all seen the pricing. You know the pricing of gene therapy is very expensive. They tend to focus on very, very limited audiences, patient populations, and that's the way that business works.

But the value is being demonstrated over and over again by third parties, and you will see that in our nomination. LENMELDY is an autologous, ex vivo lentiviral based therapy that corrects the ARSA enzyme. It's a lysosomal disorder. In spite of its name, Leukodystrophy, which it also is, it's a lysosomal disorder.

U.S. patients have been part of the clinical trial over in Milan. There's been a compassionate youth site here in the United States for several years, so U.S. patients have been treated, and that work has been demonstrated and successful here in the U.S. The sponsor of the drug has announced, I believe five other centers that they're opening here in the U.S., so they will regional centers of excellence for that therapy.

So, there is therapy. There is FDA approval. We're very excited about that, but we've got to have the diagnostics in order to get these kids presymptomatic. And in spite of the label

saying you could do early symptomatic late juveniles, we want to address those kids pre-symptomatically because no damage is better than a little bit of damage.

It is a three-legged stool though, diagnostics, the approval of the therapy, and then the access and reimbursement. And I want you to know that we're working very hard as well to make sure that the families have the access to this therapy, that they can get across state lines if necessary, and get the reimbursement through public or private payers.

I've been on Capitol Hill earlier this week. I've been doing that for well, since about 2007, and actually am a co-author of some legislation that we have co-sponsors for on Tuesday, but we're trying to make sure that the reimbursement again, expensive therapies or out of state therapies, are very challenging for our systems.

And we're making sure that that process goes smoothly. Like newborn screening it's not a straight road. It's kind of a winding road to get there. There's a lot of work to do there. With that, I just am very pleased to share or to report back and respond that as you've said, Ned, that the doors will open on May 31st, just a few weeks for nominations, and we hope to be at the top of that stack when that happens.

I look forward to talking with you more about this at the coming the August meeting. Thank you all.

NED CALONGE: Thank you, Dean, and in fact we have been talking with MLD folks, so I appreciate your presentation. Now,

we're going to turn to the internet, and I would like to invite Kendra and Keira Riley to join us.

KENDRA RILEY: Good morning. Can you hear me okay?

NED CALONGE: We can, thank you.

KENDRA RILEY: Perfect. So my name is Kendra Riley, and I'm here at our home in Phoenix, Arizona with our youngest daughter Keira. You heard from me last year about why I felt strongly to add Metachromatic Leukodystrophy, or MLD to the RUSP, but given that we now have an FDA approved treatment for nonsymptomatic children diagnosed with MLD, one of which you could see here before you, living your perfectly normal life with zero symptoms.

I wanted you to actually see for yourself why it's more important now than ever. As you may recall we have two daughters with MLD. Our daughter, Libby, is about to turn six. She was diagnosed at 18 months old, and for her it was too late to receive treatment. There were too many symptoms to make the gene therapy treatment effective, and she's currently in hospice, worsening by the month.

This is the fate of any babies born with this disease if we do not add MLD to the RUSP. One child will need to be symptomatic and diagnosed, in order to properly diagnose future siblings in time. Why would we wait one more second to add this disease to the RUSP when there is a treatment that works?

Our daughter Keira here is living proof. Because of that early diagnosis she was able to receive the gene therapy for

MLD, which is called LENMELDY in the U.S., that quite literally saved her life. She now lives symptom free. She goes to school and learns alongside other kids her age.

Keira, what do you think? What are some of your favorite things to do?

KEIRA RILEY: Going to swim.

KENDRA RILEY: You like to swim. As you can see, she's even advanced in communications, she also attends gymnastics, she's learning to ride her bike, and she loves to sing and dance to Taylor Swift every single day. All the things that our daughter Libby was robbed of because newborn screening doesn't exist for MLD.

But if it did, families like ours wouldn't have to lose one child in order to save another. And now, the very gene therapy treatment that Keira received in Italy is here in the U.S., and it has been approved since March 18th. So I can just imagine how many babies have been born since then whose parents have no idea their child could become symptomatic with MLD, and by the time they find out it's going to be too late.

So today I ask you to prevent that from happening and add MLD to the RUSP. Not only to save lives but save families from a very preventable loss that affects each of them for the rest of their lives. Thank you so much for your time and consideration today. Did you have something else to say? What would you like?

KEIRA RILEY: Playing with my sister and going to

gymnastics.

KENDRA RILEY: Just a few more things she loves to do. Thank you all.

NED CALONGE: Thanks all. Thanks Kendra and Keira. Next, we have Maria Bell, and we can see you.

MARIA BELL: Good morning. Can you hear me, okay.

NED CALONGE: We can.

MARIABELL: Well, thank you so much for having me. As you said, my name is Maria Bell. I'm a Board member of BARE, Biliary Atresia Research and Education. We are a nonprofit dedicated to education and awareness of Biliary Atresia, in advancing research and treatment for this rare pediatric liver disease, that without timely treatment will lead to significant morbidity and mortality.

Our scientific arguments for nominating Biliary Atresia to be added to the RUSP run the risk of falling flat if they have no meaning. So I'm here today to share with you the story of my husband, Ryan and I's fourth child, our son William. And so that you might imagine for a few minutes today yourself and the world of a baby with end stage liver disease.

In 2021 at four weeks old William's pediatrician here in the Northern Virginia area where we live was concerned that his newborn jaundice was persisting, and so he ordered lab work that would revealed an elevated direct bilirubin, and highly elevated liver enzymes.

Imaging and invasive testing followed, and at nearly

eight weeks old William underwent an operation that saved his life. This is an operation that not every baby is able to access in time. And even with that operation William seemed to be experiencing serious complications of end stage liver disease, and portal hypertension, anemia, malabsorption of vitamins, osteoporosis, recurrent fractures and recurrent cholangitis, a life-threatening bacterial infection.

A central line for IV antibiotics, which I managed from home became necessary to keep him stable while he waited in line with thousands of others on the national wait list for organs. He desperately needed a new liver.

As I sit here today and am talking to you, there is a mom or dad somewhere in our country holding their jaundiced newborn baby and not worried at all because they have no idea that internal disease is the reason for that jaundice, and it's fast progressing, and it's devastating symptoms will soon surface before it might be too late for a positive outcome.

There's a mom trying to comfort her inconsolable baby who's in NPO all night, had a biopsy or central line placement. There's a family taking some of their children to a friend's house while they rush their sick baby to the ER again. There's a toddler sitting in a hospital bed, a big belly, full of enlarged organs and fluid, being startled awake this morning for lab draw, but hoping for just a Facetime call with his siblings.

There's a mom or dad that will go to bed tonight making sure their phone ringers are on the loudest setting possible,

praying that the call for an organ will come. There's a mom setting up a sterile field at home, loading an iPad with cartoons as she prepares another infusion that she prays will keep her child stable until a transplant might be possible.

There's a family sitting in a hospital today, waiting hour after hour for the news that the child has survived a transplant, while perhaps her other children are wandering the halls, wishing they could find their brother and take him home. Finally, there's a mom dosing anti-rejection medication to her child, who was miraculously saved by transplant, but who now faces a lifetime of immunosuppression, and the uncertainty of life as an organ recipient.

I know these things because I have been all of those moms. An anonymous living donor rescued William from his wait for an organ in 2022, and we are eternally grateful. But I have known moms and families whose babies' stories of biliary atresia ended in tragedy, and that is why I'm here today.

Because with newborn screening we can do better for these babies by identifying them earlier to close health disparity gaps, shorten their diagnostic odysseys and bring them to treatment sooner, which in most cases can delay their needs for a transplant, a therapy not even guaranteed to everyone waiting in line.

The crux of the matter is this, that transplant is exceptional therapy for the children who need and receive it, but we want fewer children to need it. In a recent conversation, a

pediatric hepatologist, well known in our field stated that we expect 80 years of life out of every baby born, and there's no reason to not expect that for babies with biliary atresia.

So, I leave you today with this earnest plea to help us give every baby born with biliary atresia that chance, a chance that eighty years of a full and possible transplant free life, and so thank you for your invaluable work since 2003 that there's a chance for babies to survive their terminal diagnoses and thank you for listening to my comments today.

And thank you for considering BARE's nomination package to add biliary atresia to the RUSP. Do you want to say hi, William? Thank you again.

NED CALONGE: Thanks Maria. Thanks also to all our public commenters today. We appreciate your presence and your comments, and your sharing. We're going to move on in the agenda to what we didn't get done yesterday, so bring up the slides now.

So, in November 2023, we had listening sessions and received feedback from various stakeholders on the Committee's nomination process. We took feedback, we convened an ad hoc topic group that consisted of folks that recently submitted nomination packages, and we learned about the challenges that nominators experience, and got some really valuable feedback.

Then at our January meeting this year we had an open discussion with the Committee about the nomination, and evidence review process and posted the same questions in a request for information. Now I'm going to share with you some updates and

some next steps, I hope.

So, clearly the nominations are part of the grist for the mill of the work of the Committee. The challenge is there's a lot of pressure on nominators to make compelling and competence of cases for adding a condition to the RUSP. And this requires a tremendous amount of effort.

There's also a jargon that I think a lot of people in the room currently have gotten more used to but can be very daunting for most people who don't come to the meetings on a regular basis. So, our goal is to figure out ways to simplify the process for nominators but maintain the central role that nominations have for the evidence review, and our overall recommendation process.

So we had feedback from groups of five on recent current nominations. We had discussions at the previous Committee meetings, the large group listening sessions from November, and the large group discussion in January. And input from the old acting standing workgroups: follow up and treatment, education and training, laboratory standards and procedures, and then public comment we received in response to the Federal Registry requests for information from March to April of 2024.

So this is our approach that we hope we think about as being simplified, that there would be a preliminary nomination to be assessed by the nomination and prioritization workgroup that would address four questions. Is there an availability of a newborn screening test?

Is there agreement about diagnostic confirmation after a positive screen? Is there a prospective population based newborn screening project that has identified at least one infant with a condition, and then does earlier identification through newborn screening improve outcomes?

If the answer to each question is yes, then the nominators would submit between one and three peer reviewed publications for each question, and then partner with HRSA, the Chair of the Committee, and selected Committee members to assemble a complete nomination package. And this will help the Advisory Committee understand if there's enough evidence to move to a full review, but does not of course, replace the full review.

And we have some experience again, and I thank the MLD community and nominators for their time with us. I think as we put this forward, the idea is that you just have to say yes or no. So, what we did ask is can you give us a little bit more context of why you're saying yes or no, so that's an additional, what do I want to say, evolution of the process that we got by interacting with the community itself.

And I really appreciate the time that we put into that and understanding that a little bit more information would be helpful. So the advantages that we see are the preliminary nominations require much less work, and provide the foundation for having the Committee provide guidance and support about what information will be needed for a complete nomination package.

And then the complete nomination will allow advocates

to focus on key factors for moving to evidence review without having to replicate what is going to be done eventually by the evidence review committee. So where are we now? We need approval from the Advisory Committee to support and move forward with the revised approach, which will lead us in the finalization of new nomination forms.

A preliminary that we can look at, review, and then complete. And then development of additional resources, including something that came up multiple times in talking with the nominating community, a glossary of key terms, and that will lead us right into discussion by the Committee. Shawn?

SHAWN MCCANDLESS: Thank you, Shawn McCandless, Committee member. This seems like a big improvement over the existing process, actually from every perspective. I do wonder how you think about the component of requiring a prospective pilot study based on what we've heard yesterday in the public comment of the N-of-1 Rule, which whether that's really a rule or not, is currently an expectation, and would again be codified in this process.

And I guess then the question for the Committee is what information do we get from that process? What are the elements that we're trying to understand from that process, and how, what would be alternatives to the sort of a pilot study approach that would get us the same information that would be acceptable to the Committee?

NED CALONGE: I definitely have my opinions and

feelings, but I want to make sure that I don't trump anyone else's by speaking first. Jeff?

JEFF BROSCO: Yeah, just some of the historical background. So I was on the Committee, it's Jeff Brosco, HRSA. I was on the Committee when this discussion came up, and I don't know if Scott Shone is able to join us today or not, but he was a big part of that discussion as well, so if Scott's on hopefully he can clarify some of the details.

And Shawn, there was a big discussion about how the idea of proof of concept that you've taken all the way through the system, which is what's really a central part. And that yes, all components might be there, but unless you're able to actually do it, it was not appropriate for us to be raising it. That was the discussion at that time, and that's sort of where we were. Do you remember that too Michele?

NED CALONGE: As do I. Scott, your picture just came up, oh and Cindy I did see your, but since you were called out specifically.

CINDY POWELL: No, Scott was first.

SCOTT SHONE: Well no, Cindy go ahead--

CINDY POWELL: No, no you go first.

(Laughter).

SCOTT SHONE: I just wondered if you could hear me okay because I'm having audio issues.

NED CALONGE: We can hear you.

SCOTT SHONE: Okay cool. Yeah, so it's as Jeff said,

you know, I actually gave the presentation on N-of-1, before I was even a member of the Committee, so it was quite a while ago. And there were several things that we reviewed. And I think that having heard public comments in the last few meetings from several individuals and Dr. Ellinwood's comments yesterday, and the commentary that he and Dr. Gelb and Amy Giviglio have been able to pull together.

I'm happy to review it if the Committee felt it would be appropriate to readdress. I do think there's still some sampling points that are critical, you know, in my opinion of why identifying a case is important, but I do feel that in the discussion yesterday led us to conversations around the conditions for which we're now looking are becoming increasingly more rare and more rare, and the challenges of identifying one case can potentially delay the Committee from making some concrete movements forward.

I still fundamentally believe that the identification of a case in a newborn screening program is part of a perspective assessment and is essential to ensure that it works. We do this in all sorts of laboratory and public health programs. It's not just newborn screening to make sure that we're going to be able to pick these up, both from a laboratory perspective, and then from a pre-analytic processes' perspective.

So, you know as Jeff said, and you know, it's really reviewing the system impact. Not the system impact, gosh, I'm still stuck in yesterday. The system's response to identification

and the ability to identify that these cases move forward, but I wonder, and I haven't done any research into this, if you know, now what is probably a decade later, are there other things that our systems are engaged in, and what our programs are doing that we might be able to take advantage of to think about other ways to do this.

And I'm grateful that Matthew Ellinwood is in my state because perhaps when he gets back, we can talk about it.

NED CALONGE: Melissa?

MELISSA PARISI: Melissa Parisi, NIH. I wanted to also make a comment about the N-of-1 Rule, and some of the challenges that that has posed I think for prospective pilots, and also reflecting on the comments from Dr. Ellinwood yesterday, and the paper that was published and included in our packets.

And whether or not there are alternatives to that emphasis on a prospective pilot to identify one affected baby. You know, the use of retrospective pilots, and trying to incorporate data around ways that we can still test the system in a less rigorous prospective manner, and of course the issue of really rare diseases makes it increasingly difficult.

At NIH we are funding a pilot program study where we have several states that are part of our cohort, and we are trying to find that sweet spot of actually having conditions that could be part of these pilots that we would allow to adhere to these guidelines and allow for a state to identify an affected infant prospectively.

But the challenge that we have is that the timing is such that we're trying to help create the evidence base to support a RUSP nomination, at least in the traditional manner, and oftentimes those nominations in those states that would be able to do this, do not have the consent ability because the condition is not yet on the RUSP, in order for them to actually do the pilot.

So, we are caught in a catch 22 kind of chicken and egg argument, and that makes it really difficult. Very few states can actually do these types of pilots because the condition has not either been nominated for the RUSP, or added to the RUSP, and you can't be added to the RUSP until you have done a prospective pilot study to identify a baby.

So it feels like, you know, I applaud the approach to try to simplify the criteria, but I worry that that third criterion is still going to be a significant barrier for groups to overcome to be able to make a nomination. And I wonder if there might be a little bit more emphasis on the fourth criterion. I don't know if someone wants to pull up that slide again so folks can see what I'm referring to because we have a briefing book that we can look at, that I know other folks might not be able to see.

The fourth one was just evidence that an early diagnosis, earlier identification through newborn screening improves outcomes. And you know, I just wonder whether stating there is a therapy that has shown to improve outcomes as a better criterion, and that one feels almost too vague to me.

Whereas criterion number three feels too specific to

me, and I wonder if we can somehow find a little bit of a balance for this simplified approach that would be amenable to a lot of conditions going forward that are going to be increasingly rare and harder to identify that one positive case. Thank you.

NED CALONGE: Dr. Powell?

CYNTHIA POWELL: Thank you, Cindy Powell, Org Rep ACMG. One thing that I didn't see with this, you know, simplified approach, which you know I agree that there's a need for this, but in regards to case definition of what is being screened for, what form of the condition because I know that that's something that the N&P workgroup has struggled with in the past, you know, and I think that still is important for the nominators to be able to articulate, you know, because from so many of these genetic conditions you know there's various forms.

And you know we have conditions now where maybe one out of every ten infants identified in a positive screen actually has, you know, the condition that's you know really primarily the one that you want to detect early and screen for, whereas the others have much later onset conditions, or may have you know, never have any symptoms, so I think that's something important to still keep in mind, thanks.

NED CALONGE: Thanks Cindy. Michele?

MICHELE CAGGANA: Michele Caggana, Committee member. I agree with Dr. Parisi and, you know, with clarifying points three and four. I just want to caution also that by doing a retrospective identification of a case can come with some

problems.

First, as Dr. Powell said, it's not only the case definition of what's being, you know, what we're trying to detect as we move forward with that condition, but also to ensure that the patient that you're getting the sample to prove you can detect it in a newborn screening program, if you're doing retrospective, actually has the condition.

And we've had situations where we've been told children have specific conditions, and then when we test them, they really don't. And so we need good diagnostic backup with these cases to make sure that if we're going to use that one patient to make that retrospective, that we have to have the right one.

And the other thing is the issue with stored specimens, and stability of biomarkers because if you're going to do a validation and then you're going to detect, and the biomarker you have is sensitive to storage, you may have issues with that as well.

And the last point I'll make is that with the issues around residual dry blood spots and what they're used for, more and more states may be either not storing them as long or having to get consent to store the samples. And in those situations, even a stored specimen may not be available at some point.

And we can't really take an older child and test their blood either because of the changes in the biomarker concentrations over a lifespan with and without treatment, thank you.

NED CALONGE: Jennifer?

JENNIFER KWON: So I really appreciate the points that Drs. Parisi and Caggana brought up, and I think that obviously we want it to be not daunting to people who are applying, but in that bullet point that talks about nominators submitting peer review publication, and partnering with HRSA, ACHDNC Chair, et cetera there's obviously a lot of stuff in that bullet point.

And I think that for it to feel understandable to the nominators it may be helpful to put some of this excellent background in, so that people understand what they're doing. I think I had given before an example of a meeting I went to where I was, I'm not particularly interested myself, in Tay Sachs disease, I'm not a specialist in that, but I was supporting somebody that I'm mentoring.

And they had a little workgroup on Tay Saches newborn screening. And actually, they had worked with New York State to get some samples of patients who have been diagnosed with Tay Saches to look at their newborn screening cards, and they had done a lot of work, and I just pointed out that there's no treatment for Tay Saches disease in childhood.

And I mean but for them it would be really a beneficial outcome just to know the diagnosis. It's such a huge diagnostic odyssey for families to go through. And I felt horrible sort of talking about the approach of the Advisory Committee, and that I didn't really think that their application would go very far.

And I think that this idea of having a pilot, you know,

a pilot program in the state was sort of yet unknown to them, but I think they had looked at the site, and were getting started. So I think that we do need to, even though we want it to be simplified, we do really need to give the background of the criteria that we use.

NED CALONGE: Thanks Jennifer, and we are working on both the definitions. And then a frequently asked questions issue. I want to--sorry to short circuit, just to say a little bit about the N of 1, and just let the Committee know that I am a strong supporter of the N-of-1. I would not--you can know what my vote would be now.

It really comes from the original methods of development, which Nancy Green, Alice Kemper and I worked on with other Committee members. When I first came to the Committee, I started working on the evidence to decision framework. I actually proposed a provisional recommendation, and it was the rest of the Committee who said that is a terrible idea.

And I said why--because of the reasons that you talked about, you know, we can't do it because it's not approved, and so we would have to do informed consent. So I said we'll make it provisional, and the Committee to a person said we will never remove it. We'll never not do it. I thought well, we could gather data, we could get some experience, we could show that works, and it was not even close. It was like we don't have the discipline to say we're going to take it off now.

We have not removed a topic. We don't even have

methods to evaluate whether or not we're doing the right thing with the group of conditions we already have. So that's one. The second, is that we spent like an hour yesterday talking about public health impact, and I tell you, I do not believe we can understand how to implement a new topic if we haven't done it.

And so I just want folks to know I hear it. I acknowledge it, I understand the barrier that it represents, and I read the commentary, and I appreciated alternative approaches, and I just feel really strongly that this is an important criterion if we're to do our job correctly, which is to do evidence-based recommendations.

Now, NASEM is looking at the whole process, and as I listened to Jennifer, they may come back with recommendations that say you should think more about this. But I think at this point in time without a longer discussion that would go down all of the potential alleys and rabbit holes of thinking about alternative methods to the N-of-1.

I would say that we should use this for the simplified approach until we've actually created more intentional dialogue. So, I hope that, at least you know where I stand. Shawn?

SHAWN MCCANDLESS: Thank you. Shawn McCandless, Committee member. Thank you for that. Listening to this discussion it makes me reflect back that it seems to me the problem is that we have one hammer, and that to a person with a hammer everything looks like a nail, and so newborn screening is the solution to every problem because that's the tool that we

have.

And I guess I feel like this Committee needs to be persistently vocal about the need for additional tools for screening, for doing pilot studies. You know, I think that what you mentioned of a provisional diagnosis, whether Dr. Parisi mentioned about having a structured approach to pilot programs that the pilot is ongoing, and we can drop in new conditions as needed as they come up to the RUSP.

All of those things are tools that we should have on our toolbelt to really accomplish the goals of this Committee, and that we just keep getting our wheels stuck in the mud, and the only thing we've got is newborn screening. I don't know what the answer is, but I really feel that we have to be forward thinking about what else, what other tools do we need.

The second, and kind of a change of topic. For the simplified approach it seems to me that number one should be is there an effective treatment and is there evidence that early intervention or pre-symptomatic intervention makes a difference. Just so we're not being driven by the development of the technology to do the testing.

That should, it's not that anyone is more important than the other, but it seems to me that the first point should be is there effective treatment, and does early intervention--does giving that treatment in a presymptomatic phase impact the long-term outcome? Is the benefit there, and then is there a diagnostic? Is there a screening test?

NED CALONGE: So Shawn, is your idea to change the order just to not go down through the rest of the questions? Because that is what--I mean four doesn't say treatment, but kind of embedded in question four was kind of like, is there effective therapy that if it's provided early through screening detection, does it improve outcomes?

SHAWN MCCANDLESS: Yeah. I think just making number four number one would prioritize the steps in the way that they should be prioritized in my mind. I don't think it matters because this is not, you know, it's not the FDA where if you miss, well it kind of is actually. If you miss your primary goal, you don't even look at the rest of the information that you have, regardless of what they say about looking at the totality of the data.

If you miss your primary outcomes statistical significance you're done. That would be the same for this, but it probably any one of the four would probably mean that something will not move forward. Failing to meet any one of the four would, you know, would not move forward.

NED CALONGE: They're not all yes, and then that doesn't move forward. Jeff?

JEFF BROSCO: Jeff Brosco, HRSA. So to your first point, Shawn, we're tentatively planning in our next meeting to talk about what are some of the other tools out there, right? Where does clinical screening fit in, so we can draw a sharper contrast between state and newborn screening programs, and all the

other ways that we're currently doing screening that may be more appropriate for some conditions, at least at this point.

Then, to talk a little bit about the bigger questions, and Natasha has brought this up as well about what exactly is newborn screening? Is it--I'm sorry, some of the bigger questions about what exactly is newborn screening and is it as you sort of pointed out yesterday, public health emergency, this needs to be done absent this, you know, this would be considered medical neglect, not a follow through.

And we've been moving toward more and more information that would be valuable for many families, but maybe not for all families who didn't ask for it. And we're hoping, right that part of what the NASIM study will be doing this year is really digging deep into that kind of question.

Because of this, yes the eight people around this table could answer it, but it's really a much bigger question about what should do more screening be? And it might also be that that helps inform this kind of one pilot question as well. I will say at a procedural task, and our DFO will correct me if I'm wrong, that what we've been doing here is simplifying the process, modifying the way we do it, so it works better primarily for people who nominate.

Because what we've heard from them when we did those five different focus groups is we do this huge amount of work and then realize one of these is a no, and now we're struck. And so, we're trying to get to that. Yes, you have all those yeses right

away. It's worth doing the whole thing.

So this is not a real change in what the Committee has been doing, it's just trying to make it easier. I think, and Leticia can correct me if I'm wrong, if we do move away from those fundamental criteria, that's something that requires a formal vote, which requires notice, which might be the next meeting in August, which means we may have to extend the pause and stuff, so I'm just--I'm looking.

I think that's what would happen, so we need to carefully consider if we're going to make fundamental changes, we probably also want to have a broader discussion. So do we bring back, you know, Scott Schilling's presentation from a few years ago and really dig into it before we make what would be a pretty big change in our process.

NED CALONGE: Melissa?

MELISSA PARISI: Melissa Parisi, NIH. I just want to echo what Shawn had to say, and say I completely agree because when I read this current criterion for, I think that could apply to anything in which you could avoid the diagnostic odyssey.

So I do think that because that's currently not the mandate for this Committee, although we don't know what the NASEM study is going to show, and what kinds of things might be considered in the future for newborn screening. But at least with the criteria that we use now, there has to be an effective therapy that pre-symptomatic--I don't know if I'm going to quote you properly, Shawn, but that pre-symptomatically improves outcomes

essentially was what you were saying.

So, I just feel like that's really critical to be added to number four, otherwise I think it's opening the flood gates because it's not specific enough to indicate that, you know, early diagnosis could be helpful for a lot of families for sure, even if there's no treatment.

NED CALONGE: Thanks Melissa, I appreciate that. Natasha?

NATASHA BONHOMME: Good morning, Natasha Bonhomme, Genetic Alliance. One, I just wanted to note that you know I wish there was a way to have the audience members who are authors on the N-of-1 be able to participate in this conversation knowing that you all are looking at them, probably in the audience, and that might give a bit of an even richer dialogue, so I just wanted to call out that little bit.

I know that's hard to do with how the Committee is set up. But, you know, we've talked about with the N-of-1, and testing the system, but not really pinpointing what is it that we are testing, because the newborn screening system is tested every day, hundreds, thousands of times a day because babies are screened every day.

So, what are those particular datapoints that have been so helpful within the context of making a decision? Maybe calling those out, or being able to parse that out, you know, I'm assuming it's not necessarily all of the preanalytical work that I just mentioned because again, the system is tested every day.

I think just getting a little bit of clarity on what exactly it is that we've learned, and maybe doing a little bit of retrospective on conditions that have been added, that did go through those pilots, and what made that so helpful can just help us all know what is it that we're actually talking about, and what is that value, thanks.

NED CALONGE: Thanks Natasha. So I'm going to try to--oh sorry, Ash?

ASHUTOSH LAL: Just a quick comment on I think the, Shawn, I think the focus on point four and I think a little more clarity with the presentation from FDA yesterday was extremely helpful for all of us. And I felt that in some cases when you're saying there's a treatment, effective treatment, available it's equated with an FDA approved therapy.

But as we learned yesterday that the approval puts in the accelerated pathway, actually implies that the efficacy has not been proven at the time of the approval. So that what I would be, and I hope the other Committee members will be looking for, is how that FDA accelerated approval was used to then prove that the treatment was effective.

And we don't necessarily have to wait for, for a particular approval later on, so that could take a much longer time, but there should at least be preliminary evidence that the accelerated approval led to an approved pre-symptomatic outcomes. Thank you.

NED CALONGE: Thanks, Jeff?

JEFF BROSCO: Jeff Brosco, HRSA. So following up on Melissa's excellent suggestion, just a slight wording change for number four, if folks are okay with it. So, keeping a lot of it the same, earlier identification through newborn screening leads to interventions that improve outcomes. What do people think?

NED CALONGE: I'm still concerned that until we flush out interventions other than effective therapy, that we haven't been specific enough about what we're looking for about how we used to look at it, or how we currently look at things. Do you understand what I mean?

So, there's an effective therapy that improves outcomes if given earlier. Shawn?

SHAWN MCCANDLESS: I think we also need clarity about who the outcome needs to be affecting, so is the outcome to make the life of the baby that's being screened to improve the outcome for the baby, or are we leaving it generic so that to allow for improving the outcome for the parent?

NED CALONGE: Another great question. I mean where we are today, and we heard talk about it yesterday is it's a benefit accruing to the individual. Chanika?

CHANIKA PHORNPHUTKUL: Chanika Phornphutkul, Committee member. I just want to echo what Dr. Lal just said, especially since I noticed that most of the more recent FDA approval are on an accelerated path, and there's really no easy way to translate that into clinical improvement.

So, I think we do need to think about that, and then

have, you know, sort of information to see that newborn screening will improve the child's life if that's the goal of this Committee. Thank you.

NED CALONGE: So, yeah, so the accelerated pathway adds a level of complexity. We don't actually equate FDA approval with effective therapy. We do an evidence based review, and then we make a judgment based on the evidence review, but this is for the nomination, and so I guess the issue is would we let--by saying, by thinking about FDA approval as an effective therapy through an accelerated pathway, would we bring more conditions in that we would then later say no to after a full evidence review?

And I guess I don't know the answer to that, but it does say we would start the machine. We might start the machine working short of knowing that we have an effective therapy. So Jeff, you seemed resistant to the effective therapy wording?

JEFF BROSCO: No.

NED CALONGE: Okay.

JEFF BROSCO: I changed it already.

NED CALONGE: Okay. So I'm going to again try to summarize. So we didn't notice this. This is just kind of like we are in favor of the direction we're going, and we'll do a little bit deeper dive with a formal vote at the next meeting. The things I've heard are we want to add effective therapy to number four.

Whether or not it needs to be one or four, I'm a little bit agnostic, but if Shawn feels strongly, if not then I think we

can go. And then I would like to just raise up this issue there's a clear case definition. I will tell you that that's something that the USPSTF puts as a very first question is do we know what we're screening for?

And so I wonder about does that add a level of complexity to the nominators that is unwarranted or warranted? Should we add a question is there a clear case definition for the condition for which we're recommending screening? Shawn?

SHAWN MCCANDLESS: You know I'm going to have an opinion about everything, which is why people from HRSA are happy to see me go. I think that that's absolutely critical. I think there has to be a case definition. I think what we saw with the process with Krabbe disease, that was really a very important issue that eventually led to the Committee moving forward, was when there was an agreement around the case definition.

You know, Krabbe, that condition raised many important issues over the years that were addressed, and as frustrating as it was for the nominators that it took so long, it really does show that the process can be effective in getting to a conclusion. But I do think that case definition needs to be in there.

Maybe as, my first impulse was to say add it to number two, that there's agreement about case definition, and there is an acceptable diagnostic, or an effective diagnostic confirmation process.

NED CALONGE: I like that suggestion. I'm thinking about MLD, and I don't think this is going to be an issue for that

nominating group, so I'm really trying to be sensitive to moving ahead at the end of the month with this nomination. I think it's really important for the community as well as I think our group. Michele? I'm sorry Melissa, I'll get back to you.

MELISSA PARISI: Well, I just wanted to ask if we end up voting on this in August does that mean that you're not going to open up nominations at the end of this month?

NED CALONGE: No. We're going to kind of if everyone is kind of in favor of where we're at, we're going to move forward. If people say no, we want to revisit, because this is consistent with what we do. If want to change the criteria completely for a nomination, which these four questions are based on, then we'd have to extend the issue.

And I think adding case definition doesn't change what we currently do. Thanks for the question though. I really appreciate that. Michele?

MICHELE CAGGANA: Michele Caggana, Committee member. I agree with case definitions, and I think it's really important, and as several of the past nominations have shown that it really helps newborn screening programs implement when we have a clear definition of what we're screening for.

And I think you just need to be aware that's going to feed into the N-of-1 because if you find if you don't have a good case definition, and you find something with your screening test, have you really found it or not? So, they're sort of related.

NED CALONGE: I appreciate that. So with those kind of

two changes I'll just review them again. One is adding case definition, either a separate question, or probably easier just within question number two, and then adding effective therapy that outcomes are improved through earlier identification with those two changes, are we okay moving forward and working with and it wouldn't, I'm just saying MLD, but I know that one is there.

There may be others that are waiting for us to kind of say bring one in. Shawn?

SHAWN MCCANDLESS: I'd like to propose--I don't mean to trump Jeff Brosco of course, but I want to--I would propose language for number four that says earlier identification through screening, rather than clinical diagnosis allows provision of the effective therapy to improve the outcome for the infant screened. I think that captures all the points that were raised.

NED CALONGE: Does that sound okay to other panel members? Okay. I think we're good. All right. Oh, Margie, I'm sorry. I got so excited about coming to an answer, but.

MARGIE REAM: Not to complicate number four even further, but just looking for a little clarification on the wording that earlier identification such as could be accomplished through screening, or are the nominators supposed to demonstrate the screening itself, you know, has been effective in approving outcomes?

So for example, the cases of, you know, pre-symptomatic diagnosis through siblings demonstrates the point of what newborn screening or other screening could accomplish.

SHAWN MCCANDLESS: Margie, I think that's a great point. I do think the way I worded it could be interpreted to mean that only newborn screening followed by evidence of effective intervention leading to better outcomes would be acceptable, and that's not what we're trying to accomplish here, right?

NED CALONGE: Such as through newborn screening?

SHAWN MCCANDLESS: Yeah. Or maybe presymptomatic diagnosis rather than clinical diagnosis allows the provision.

NED CALONGE: Yeah. Okay. Okay. I think we're good. I'm not seeing body language or nonsmiles from people I'm looking at in the group, so I appreciate that. Oh, Ash?

ASHUTOSH LAL: I'm not so clear about number four. I would just like to see the language written not just to think about it so that it doesn't look--

NED CALONGE: Okay. We're not taking a formal vote. We'll get it after lunch. Yeah, give me a chance to type that up, good. And I'm looking at, you know, I'm giving Shawn and Margie the top going over and making sure it says what you think it should say, okay. Thank you. This has been--Jennifer?

JENNIFER KWON: Darn it I'm sorry. Jennifer Kwon. I was in a group with people who had submitted the CMV nomination, and so I just -- and I was trying to bite my tongue the whole time, but I was just kind of curious if there was something that we needed to share about the test, because I think we heard some things about how long they had spent on the application, and there is -- I think in their mind, a newborn screening test that doesn't

feel like it's a good newborn screening test in our mind.

And maybe the simple sight approach you can hash that out with them, so that that's fine, but I just wanted to share that.

NED CALONGE: I appreciate that, and that is indeed the intent and hope. Okay. I think we're going to break until 12:30, and you all earned it.

Lunch

(Lunch break.)

Newborn Screening Ad Hoc Topic Groups: Updates and Committee Discussion

NED CALONGE: Okay. Ash, we have identification before clinical presentation allows provision of effective therapy to improve the outcomes for infant screening. Oh, and the case definition of diagnostic confirmation, so those are the two additions.

I would suggest we go with this and see how it works. And if we have to revise it, we can revise it.

ASHUTOSH LAL: If we can send comments by email later on.

NED CALONGE: That would be great.

ASHUTOSH LAL: I think for--I would like us to think about--

NED CALONGE: I understand. Yeah, this is important,

and I appreciate that. Okay. Home stretch. I think we're going to start the afternoon, the after-lunch session with updates on activities that we identified as important to the ad hoc work groups.

These are occurring through our partnership with APHL, and we'll now get information on those topics such as health equity community of practice, follow-up and education group, examination of higher tier testing group, also known as second tier testing.

Counting of and naming convention for newborn screening conditions, and other NBS screening updates. We are very happy to recognize and ask to come up and provide us some information, Jelili Ojodu, who is just recently back from the APHL meetings. Thanks for rushing back.

JELILI OJODU: Thank you for the invitation. Good afternoon, everyone. All right. Let's see here. Is there a clicker? Perfect. All right. So over the next 90 minutes or so, thank you again Dr. Calonge for the opportunity to present to the Advisory Committee. It's always a pleasure.

This is supposed to be a discussion/dialogue with the Advisory Committee on activities that we are embarking on, not just as Newborn Screening Excel, or NewSTEPs, Newborn Screening Technical Assistance Evaluation Programs, but as a program that is managing, and a membership organization program that at least in my part, looks to address a newborn screening related activities for our members.

And we're now going to well, at the prerogative of the Chair, I think there is the presentation is broken into a number of sections so at the end of each individual section I think there will be a time for questions and answers, or comments in between. We're funded by HRSA. All of the activities that I'm going to talk about today is going to be HRSA funded related activities.

This is a funding opportunity that we've had for the last 13 years ongoing, and this is the 25th anniversary of HRSA funding a comprehensive newborn screening resource center, not us for 25 years, but for the last 13 years.

So, at the Association of Public Health Laboratories, the way that we manage the activities on behalf of our members is through Committees, Subcommittees, workgroups, ad hoc work groups from the funding that we get from HRSA, we manage a number of activities, and this is just an org chart of some of the things that I'll be highlighting.

Certainly, there is the NewSTEPs Steering Committee, they advise us on a number of things that we do. And the NewSTEPs Steering Committee as you can imagine again, we think of the newborn screening system. And so folks in that system are pretty much the folks that are comprised of any one of these Committees, Subcommittees and workgroup.

Our large Committee, as we call it is our Newborn Screening Committee. On the right-hand side, which is invisible to you all right now is activities that are also funded by CDC, which are not shown here, but we certainly have a number of things

that we do with CDC through funding cooperative agreements, again for almost for the last 25 years.

I'll be highlighting activities related to follow-up, not only because it's important, because there has been a sustained lately, funding for state newborn screening programs to be able to highlight and address follow-up, whether it's long-term or short-term follow-up in those programs.

You heard from Dr. Calonge about the higher tier, and sorry I missed the discussions that occurred yesterday, but I'll definitely be watching that in the coming days, or whenever it's available. I'm going to talk a little bit about higher tier, second tier, any kind of tier that is done after that first tier that it may be necessary to reduce false positive or identify that newborn that we want to get into a medical home as fast as possible.

Condition counting, we'll spend a little bit of time talking about it as well, and education. The things that I won't talk about, but it's important to note is that we also spend a good amount of time addressing needs related to health information technology in newborn screening.

We spend a good amount of time discussing and addressing continuous quality improvement, having a, you know, CCHD is still on the recommended uniform screening panel, and addressing that through a data response team. In the, I guess, new disorder is where will newborn screening be without new disorders in one way, shape or form.

Addressing the challenges, opportunities and how states can implement whatever condition that they've added to their own state panels. So, the things that are highlighted on the left of the slide is what I'll be highlighting primarily here.

One thing that I didn't add on the slide that I will be highlighting briefly is the fact that through HRSA funding, through a supplemental fund that we receive from HRSA, thank you very much, we are embarking on a multi-pronged approach to address something that we know is important.

Something that is part of HRSA's blueprint, something that we know that certainly needs to be addressed as part of our newborn screening community, and that's advancing, or looking at the health inequity in newborn screening. So, the funds from HRSA as a supplemental. We are trying to do a number of things.

Doing what we do best, which is bringing together folks as a community of practice to be able to discuss openly, freely, with some boundaries, the issue about health inequities as it relates to newborn screening. The why's noted on this slide here I don't need to highlight it other than the fact that most newborns get newborn screening is the only thing that is common for those newborns.

We know that there are a number of disparities in throughout the newborn screening system, and I think it was a couple, or maybe a year ago now that there was a presentation to this body by the Dr. Houtrow from I think University of Pittsburgh, who did a fantastic job on highlighting at the highest

level, but she drilled down even deeper into some of the things that we should be at least considering as we move forward.

That, among other things, was the impetus to say we can take at least the lead in this multi-prong approach, working with partners in developing the community of practice, talking about real issues, and then training opportunities with folks that have, you know, not only do this for a living, but bring this back to our own newborn screening system.

And then ideally, we'll have the opportunity to present to you all at the request of the Chair, some of the updates on some activities that we've embarked on in the near future. So, it was several months ago that we launched a listserv or collaborate as we call it at APHL where folks can join.

I wanted to add everyone from every state and every part of the system that I was told they probably overwhelmed with all of the other things and the services that they're a part of at the moment. So I have about 100 folks that have joined. If you're interested in joining this particular community of practice, just email us, or let the DFO here know, and we will make sure that you get on that particular listserv, but there is --that's really it.

And there's been some really good discussions. That's why in just level setting, but understanding in fact, what do we mean by health equity in newborn screening, as it relates to newborn screening. We plan to collaborate with the Regional Equity Institute in developing a number of training opportunities

for folks in the newborn screening programs.

And just like we've done in the recent past use our data from NewSTEPs data repository to highlight and figure out how we can better address some of these disparities that we've seen as it relates to different variables, so that's timeliness of outcomes, and other variables in order to be able to address this, so more or less in the coming months.

And with that I'm going to pause, and this is going to be the way that all of the other kinds of aspects are going to go if they are any discussions, so.

NED CALONGE: Questions at this point? You've been so clear so far.

JELILI OJODU: Follow-up in education.

JEFF BROSCO: So, Jeff Brosco, sorry. Just to point out as you were saying Jelili, this is funded through a supplement through HRSA, so just a reminder that in the four pillars of the MCHB strategic plan, equity is one of the key ones, and so this is one of the ways that we're demonstrating that through our funding.

JELILI OJODU: Thank you, Dr. Brosco And we really do appreciate that. It does take a lot for the federal agency to say that this is important, and certainly will be taking that mantel moving forward. So follow-up in education, I don't think I need to say more related to follow-up, but I will.

Because of the funding opportunity that we got from HRSA to be able to stand up Newborn Screening Excel, which is NewSTEPs, and the opportunity to be able to develop again, the

community of practice for follow-up. We've been able to do a number of really, really fun things with this community, including among others, strengthening the system, providing guidance, tons of webinars, a forum for communications, for folks to be able to have a home.

I don't know where the follow-up home stands when it comes to newborn screening systems. And I think it's a little bit weird for it to be as part of the Association of Public Health Laboratories, but it's not weird because we think about newborn screening as a system, and in fact it's certainly beyond the fact that there are a number of aspects of the newborn screening system that needs not only assistance, but you know, just some kind of identity.

The short-term follow-up workgroup, among other things, also identified needs of different programs to be able to provide technical assistance, and other kinds of activities. With Newborn Screening Propel, which I'm sure you've heard quite a bit of over the last several months, at least.

The funding for Propel in those Propel states, I think they had one of two things to be able to address implementation, or additional new conditions to their state panels, or whatever that is going to enhance that, and an increased emphasis on a long-term follow-up, or follow-up to be general.

I think it goes without saying that I believe that this is the most amount of dedicated funds when it goes to long-term follow-up that is going to state newborn screening programs to be

able to expand, enhance those program capacities and capabilities. Again, kudos to HRSA for that.

As part of this long-term follow up workgroup, we're going to do a number of things. One, is to understand the continuous evolving landscape when it comes to long-term follow-up. Five, ten years ago I think a number of folks would say the intubation of long-term follow-up in state newborn screening programs, and addressing those kinds of activities should not be part of long-term, should not be part of state newborn screening programs.

Now, we are seeing more and more states not only invest in long-term follow-up, but they're thinking about how they're going to be able to sustain their long-term follow-up programmatic activities in the near future.

I know this has been done quite a bit of times, but ideally once and for all we want to be able to define the essential elements as it relates to long-term follow-up. For those state newborn screening programs that want to be able to collect it and include it as part of their newborn screening programs.

With the number of newer conditions that have been added to the RUSP I think it's inherent that's it's not only important for states to be able to figure out how they're going to address long-term follow-up, but in some cases a number of other states need the opportunity to demonstrate the value of this, and helping them do it in the ways that we've done over the years,

whether it's a white paper or a fax sheet, or any one of those other kind of tools are things that we're going to be working on in the coming years.

And then for our own sake, as a data repository, and certainly for HRSA as one of the things that they've requested of us, develop quality indicators similar to all of the other kinds of quality indicators that we collect. Education, and I think this is being covered here that I can't see what that is--I can see it on the screen, education workgroup.

So, in collaboration with expecting health, we are, and we've had a long-term, and we've had a long-term professional wonderful opportunity to work with, whether it was Baby's First Test, and now Expecting Health, both programs that the Genetic Alliance, to work with states and other families to be able to develop and understand a landscape of the needs through a needs assessment.

Continuously find ways to engage families and share their experiences on all of our Committees, Subcommittees and Workgroups. You know, sometimes that can be difficult because I think sometimes stories are individual, but I think the collective of these individual stories do inform us as a collective on all of our programmatic activities.

And then find the ways to be able to evaluate, not just the newborn screening community, but other providers serving medically underserved and historically excluded communities. I'm not sure when exactly the survey is planning to go out, a little

fuzzy, but I think it's we've been working on this for the last several months, and I anticipate that a survey will go out to the newborn screening committees within the next several months.

The highlights of all of these activities and workgroups will be presented at a later date to you all. This is a way to show, I'm not sure if you can see this in the back, but to highlight that for every workgroup there are individuals, part of the newborn screening system that lead the effort to be able to affect change in one way shape or form.

I haven't talked about counting conditions yet, I'll get to that in a little bit for higher tier, but at least for me this is a way to show sincerely appreciation for all of those who take the time and effort to be part of a solution, a solution in dealing with a number of challenges that we faced in the never-ending complex system that we call newborn screening at this moment in time.

I think we've highlighted the Committee Chairs for each one of these workgroups, and certainly appreciate all of the effort that goes into these activities. For the ad hoc workgroups, I think you would notice that we've added Advisory Committee members to be part of that, to be able to not only bring information back to this group, but also share their thoughts in the different number of hats that they wear.

So, I think I've talked a little about this. I'm just going to highlight a few things in that this is a great opportunity to redefine long-term follow-up and working with not

just two states or four states, but dozens of states, to be able to create a lasting effect of what long-term follow-up should be is something that will be under our auspices in moving forward.

Engaging of the community, working with different folks in the newborn screening systems, and presenting them in national webinars or our symposium. Demonstrating the value of long-term follow-up, and I know this Committee has talked about quite a bit the importance of outcomes. Outcomes for all of the conditions that we've been adding to the recommended uniform screening panel, long-term follow-up and the collection of those kinds of data and coming up with measurable outcomes that we can collect in the future is going to be key, and that's what we're going to be embarking on. So with that I'll stop.

NED CALONGE: Questions? Hi Melissa.

MELISSA PARISI: I guess I just want to ask the question, I'm feeling a little bit like Shawn McCandless, because I feel like I ask this question every time, but how are we defining short-term and long-term follow-up? Because that's always a question that I am always curious about, and I'm just wondering if there is a precise definition you're using for these Committees, thank you?

JELILI OJODU: So, that is a great question. And in fact, I went against something that I normally don't do. I normally would love to just call it follow-up in general, not long or short-term follow-up. But the fact that we just haven't spent enough time on long-term follow-up means that everything that is

done right after the baby is called out is what we define as short-term follow-up.

The longer-term follow-up is that anything after a certain number of either time, years, you know, how can we collect informable data to be able to highlight or show that what we're doing in newborn screening, the condition that we're screening for is actually what you set out to maybe recommend or approve on these conditions?

I think the answer to your question we'll leave to the Committees as part of their definitions moving forward, but there hasn't been enough, well concerted efforts to be able to address long-term follow-up up until the time that HRSA then funded the states to be able to do things, and I see that Dr. Brosco probably wants to add a few points there.

JEFF BROSCO: Yeah, just a quick point of information that the workgroup of this Committee we had a report, and I forgot how many years ago, it's now three or four at least. And we tried to change it to longitudinal, so that we didn't get caught up, and some people's long-term is three years, and some is 30.

They also laid out a whole bunch of ideas about how this could be done, and I think this workgroup is following up on the work that we all did some years ago.

NED CALONGE: I'm going to go to Michele first, and then Ash.

MICHELE CAGGANA: Michele Caggana, Committee member. I

just wanted to thank HRSA and APHL for paying much more attention to follow-up. We always talk about the newborn screening system, and a lot of times that relates just to, you know, people then just talk about the lab.

And then a lot of states probably, most people in the audience are aware, but in a lot of states the laboratory and the follow-up operate on different spheres with different chains of command, and this is a way to help bring that all together, and really focus on helping people in the follow-up community come together and share ideas, and work on long-term follow-up, which we've all talked about for probably my whole career, and is finally really getting off the ground more, so thank you.

NED CALONGE: Ash?

ASHUTOSH LAL: Sure. I think the first topic that you had presented on disparities and inequities, I think that the framework for thinking about that even more than the initial laboratory tests is the--I think the long-term follow-up is probably where we would find the biggest challenge to ensuring that we have health equity, and that that's the place that's most likely to get uncovered.

And all the effort that goes into it in defining an infant who has a condition that can very easily be compromised by the systems under which long-term follow-up has to operate. And it's subjected to the same kind of--many of the same obstructions that other medical conditions have.

But to the extent that there's federal funding for a

lot of patients that are on Medicaid, some of them are, what is the interest in ensuring that access to specialty care is preserved, which is what is needed for many of these, if not most of the conditions that are identified, and restrictions to either insurance, or to graphical areas or county line, or state lines, can be reduced or minimized.

NED CALONGE: Jeff?

JEFF BROSCO: Jeff Brosco. I'll try to take you off the hook on that one Jelili.

JELILI OJODU: I wasn't sure if that was a question, or more of a--

JEFF BROSCO: So Ash, this is a wonderful question, and it gives us a chance to talk a little bit about, you know, why we're moving toward the Propel, and soon to be announced CoPropel.

JELILI OJODU: Right.

JEFF BROSCO: July 1st we should be announcing the CoPropel winners today, and our goal is to support as many states as we possibly can to do new conditions, short-term follow-up and long-term follow-up. And this came out of our blueprint, just to backup, so everyone can remember.

The blueprint was a couple years of working with families, stakeholders, inside and out of government, and we heard primarily from families look, you can be doing all this work, but if it's not having real impact, if we're not seeing benefit to families and children, then why are you bothering with all of these activities and really trying to make a system of care work?

Exactly what you're talking about.

And so, we've been examining all of our programs. Our newborn hearing screening, and newborn screening in particular, saying it's fine to identify the child, but they don't go on to get all the care they need and thrive, then the screening didn't help as much as we thought, so this is part of that broader idea.

And we also have a number of programs working with AAP our grantee on the blueprint consortium implementation, to look at the largest system of cares issue because it's not just for children and newborn screening of course, it's all kids with any chronic condition.

So, there is a lot of work going on, and the Propel, Co-Propel is the specific newborn screening part of it. I'll also say that our regional genetic networks are ending, right? I'm sorry. And this is sad for all of us, but we decided it was really critical to take those resources and put them into this sort of systematic approach to improving outcomes for all children. So, your question was exactly right on, thank you.

NED CALONGE: Debbie?

DEBRA FREEDENBERG: Yeah. So I just wanted to say that on the long-term follow-up, obviously there have been a lot of years of discussion in this short-term follow-up, and to appreciate taking on the huge cultural shift that this is going to require in a lot of newborn screening programs and states.

Because up until recently a lot of the programs were feeling that this was not in their purview, and that this was

clinical care, and they were public health, and were not going to get involved in it. So I just wanted to add another voice to say thank you for taking this on and trying to improve the system.

JELILI OJODU: Thank you.

NED CALONGE: Michele?

MICHELE CAGGANA: Michele Caggana, Committee Member. Also just wanted to let this group know that if they're not aware that the CLSI group has come up with, getting back to definitions, they have developed a bunch of terms around newborn screening, and so it might be a good thing for people to take a look at, and so we're all talking about the same thing, defining it the same way. CLSI. Clinical Laboratory Standards Institute.

NED CALONGE: Robert?

ROBERT OSTRANDER: Thanks, Robert Ostrander, AAFP. I just want to expand a little bit on what Jeff said, and when you're collecting information, in the long-term follow-up, on longitudinal follow-up and treatment workgroup, it became quite clear that there were two aspects of that.

One was the outcomes thing that you mentioned, which by the way I wondered if for these more rare conditions it might actually be easier to get the outcome side, because the registries are going to be small. But the other part is the structure of what the longitudinal follow-up looks like.

I'm not--you know, I don't think it's necessarily in your purview to recommend what that should look like, but it would really be good if part of your dataset wasn't just what the

outcomes were, but what does the care look like in different places, because you know, it's a constantly evolving issue.

And care coordination between the primary care piece, and the specialty piece is a conundrum, and it would be nice if there was some place where there was a landscape survey so that people could look at it, and perhaps you know, get some lessons learned in developing.

So I would suggest there ought to be two datasets, if you will, of long-term follow-up. What are your thoughts, or is that already your plan?

JELILI OJODU: No, we have not. We spent, I think this is our third month of actually discussing these things, so three 90 minutes, or hourly calls. These are good things to be able to take back to the workgroup though, knowing that we want to be able to address reachable goals immediately through our funding opportunity with HRSA, to be able to demonstrate that not only can it be done, I'm totally convinced that the Committee of practice that we are fostering is going to be able to not only provide and guide us, but tell us exactly what they need.

But certainly, bringing this to the Advisory Committee, and then getting some input about what additional thoughts or data, or ideas should be brought into play, so to be continued with, just too early to be able to get there yet.

NED CALONGE: Great, higher tier testimony.

JELILI OJODU: Higher Tier. I don't think I need to spend too much time on the background, but it's on the slides

here, and many thanks to my colleagues who developed these slides for me to present today. But it's become even more important to be able to not only provide, highlight, demonstrate, that second tier or higher tier testing is needed for some of the conditions that we're screening for.

And similar to the other things that I had mentioned in the previous discussion demonstrating the values to some folks in leadership, you're doing screening, you're doing first tier, why isn't that enough in making sure that the baby gets into the medical home? Why do we need a second tier? Why do we need that additional cost on those, you know, not that many specimens to be able to do that. And again, in light of some of the recent conditions that have been added to the RUSP where this group is not only suggesting the case definitions of those conditions, but in fact saying that we want to pick up the early onset.

And the only way that we can pick up the early onset is with one of these higher tier tests. I think it begs the question then, you know, why aren't we all doing this? Well, that's why we're here to be able to harmonize things, and to make it easier for them to be able to do this.

This came up and I think we can take credit here. This came up as part of the lab's subcommittee's activities that one of the subcommittees of this Advisory Committee that you all have been meeting for years, but, and then it got punted to us as APHL to be able to then move forward as an ad hoc workgroup, building a number of model practices, and a model collaboration for folks to

be able to enhance and expand their capacities to be able to bring on higher tier testing.

Again, and I should say this again, most of these work groups started at the end of 2013, I mean 2023, I lost a decade there. And so, we literally, I mean it's great that I'm here presenting all of this, but I anticipate that in the very, very short amount of time that we hope that we'll be able to have concrete information, tangible things that we can then say that we want to be able to move forward with.

The objectives of this higher tier workgroup are listed here, but it's to also demonstrate and examine the landscape of higher tier testing in newborn screening programs across the land. Be able to then describe again, it sounds easy, but we really do need to be able to describe and prioritize why it's important to have the utility of that tier testing.

Highlight those existing models of collaborative, identify barriers. It takes, and I know this for a fact, first from some states, it takes 18 months to two years to be able to get a contract regardless of where you're sending it out to, whether it's another state, or one of our commercial partners to be able to do higher tier testing.

You know, so it's not like the state is not trying to, but those barriers, now we can be able to inform decision makers on these kinds of issues is important, and ensure these models have practices across a newborn screening program. For everything that I say here I should also highlight that part of what's under

our charge is also to be able to develop, for lack of a better word, a marketing plan.

How best are folks going to be able to digest this, and be able to then affect change as soon as possible? So, more to come on that, but the desired outcome is listed here to determine barriers to sustain across state collaboration for higher tier testing, and solutions to be able to improve that positive predictive value, and then obviously, coming back here to be able to present all of this to you all.

We met, they met, a few times, and I think I'd be remiss if I didn't highlight Dr. Dizikes is in the audience here, who is one of the two Co-Chairs of this particular workgroup. I probably will be punting any hard questions to him, but at the prerogative of the Committee Chair for him to be able to speak.

But thank you to HRSA again for funding this opportunity to fund them to also to come together for a discussion. We'll be meeting sometime in the D.C. area at the end of July. And then, again there are developing surveys, they're developing barriers and challenges. They're developing how we're going to be able to market and figure out and highlight who does what.

How many states, or how many entities do Psychosine testing for the condition that you just added to be, well sorry, the condition that has been voted on by this body recently, and I don't think it has been added yet to the RUSP. For folks in any state to be able to see and know immediately, this is what it is,

and this is probably the cost, and this is what it's going to take for me to be able to do that.

We'll be hosting a number of listening sessions and webinars in the coming months on how to be able to address those challenges, and I think I'll stop there.

NED CALONGE: Melissa?

MELISSA PARISI: Melissa Parisi, NIH. I just have a question for states that do screening and have send outs for some of their secondary, or second or third tier testing. Do the states every bond together and negotiate contracts with some of the specific testing laboratories to try to get a reasonable rate given the fact that hopefully these tests are going to be relatively uncommon, but you know, you're going to be regular, kind of repeat requesters, so I'm just wondering if that negotiation ever comes into play?

JELILI OJODU: I can--I mean there are a few of them in the audience here. It's, Dr. Parisi, that question is I mean I think states do talk to each other when it comes to getting the best deal for either the first tier, second tier, or whatever. However, it's almost always very difficult to be able to look at how you can get the same kind of bargain from one state to another.

It's a package, it's the number of screens, it's the number of babies. It's, are you ordering paper from that manufacturer? Are you, you know what else do you have that's part of the deal. The good thing is that there are a limited number of

states or commercial entities that provide these second-tier tests, and they are almost always readily available to be able to communicate, and reach some kind of deal with the state to be able to do the test.

That said, there are two, at least, states that are in the audience here that maybe can share their thoughts about your question.

NED CALONGE: Susan?

SUSAN TANKSLEY: Susan Tanksley, Organizational Rep for APHL, and I'm with the State of Texas Newborn Screening Program, and I think it's an interesting concept, and I wondered Jelili, if there might be an approach through the workgroup similar to like public health pricing that's been achieved with some of the manufacturers for equipment.

I don't know if that's something that the higher tier workgroup could do. Typically, the contracting process is very difficult for states, and so if there would be some way to streamline that process. Unfortunately, it's the, you know, 53 newborn screening programs all with different rules for contracting too, that plays into the difficulty of that approach. I think it's a great idea if we could figure out how to do it.

NED CALONGE: Scott, is this on the same issue?

SCOTT SHONE: Yes, Doctor. Scott Shone, Org Rep for ASTHO. I agree with Susan. I will say that you know the biggest barrier to cross jurisdictional types of agreements, whether they're procurements or MOAs about operations or terms and

conditions, and once counsels get involved the terms and conditions between states vary substantially in there are statutory requirements that certain states have that other states don't.

And so, what I would like to suggest that if that is something that either APHL, one of our work groups generally, or the Committee wants to pursue the National Association for State Procurement Officials, NASPO. They are responsible for--they are the organizational group for all the procurement officials across each state in the country.

They do negotiate large contracts, for example, with some of the commercial carriers, overnight carriers, and many states sign on to those agreements, and so when the NASPO contract with UPS expired last year, it was a pretty important impact on all programs, both newborn screening and otherwise in public health, and then that had to be renegotiated, so basically states could sign on to that.

That might be an opportunity, you know, because these are competitive bids and it generally said there are pros and cons to having a limited number of vendors in a competitive market for the same service, and so but it's going to be incredibly difficult for a large group of states to negotiate and agree on terms and conditions, but the NASPO path might be an option.

NED CALONGE: Thank you Scott. Shawn?

SHAWN MCCANDLESS: Shawn McCandless, Committee member. I'm wondering if you could comment on whether there's any

anticipated impact from the FDA's rule change regarding laboratory developed tests, and what the impact of that may be on the relatively small number of labs that are offering both state labs and commercial labs that are offering second tier tests for newborn screening.

JELILI OJODU: Thank you Dr. McCandless. So that is actually one of the other slides that I have made later on, and I hope to be able to get to it in the near future. I will say this about the new 533 page report that just came out is that I have not spend enough time looking through it. And our organization, and I'm sure a number of organizations are doing the same thing right now, figuring out how this is going to impact for us, at least, newborn screening and genetics.

I will say though that this is something that's going to be important for this body to be able to not only address, but figure out the implications, especially for these newer conditions. There are things that I believe have been grandpersoned in before May sixth, things as in conditions, or the testing for those activities.

And even with those, there is limited amount of oversight from the FDA over the next three to four years for those. For future conditions that require or either an FDA approved kit for the newborn screening program to be able to bring on, my personal thought is that it's going to take a little bit longer, or the investments in the state newborn screening programs, hopefully in collaboration with the Centers for Disease

Control and Prevention, with our friends at FDA, with our commercial friends, to be able to figure out an FDA approved assay for some of these.

It's the requirements on states, and not all states can be like the great State of New York when it comes to those kind of developmental activities. It's going to, in my opinion, limit the availability of the immediate availability of tests as we have done in the past, so that's a short answer to the long question that I've read it, our organization is working on a quick overview of the implications to not only newborn screening, but infectious disease and other kinds of things as it affects our community.

But there will be a change, and someone has to be able to pick up the mantle of developing these tests. That is going to be brought up to this Advisory Committee for suggestive or inclusion in the near future.

NED CALONGE: We look forward to the APHL cliff notes, thanks. And Jennifer?

JENNIFER KWON: So, Jennifer Kwon, Committee member. So as someone who is not really very close to the laboratory processes, but for whom higher order testing really is profoundly helpful in determining the severity of the condition, how quickly we need to manage a condition.

I was just curious if there was any mandate to hold, to sort of adhere to the RUSP guidelines, for example, with Krabbe disease for their cutoff, because we already have states who don't have the cutoff in place. And that may not even be part of the

scope of this ad hoc group. I'm not sure what the consideration is.

The other topic that comes up frequently, at least in neuromuscular clinician meetings is the value of being in a state that provides SMA2 copy numbers when we receive our SMA referral. It is incredibly helpful. I cannot overestimate how important it is for us to know that we're going to be getting a baby with two copies because just the language of what we say on the phone is quite different.

JELILI OJODU: Yeah.

JENNIFER KWAN: So I think like that I just wonder if there is any opportunity to loop in clinicians who are seeing this information, rather than having to primarily be a group to help standardize and refine the laboratory techniques and turn-around time.

JELILI OJODU: Yeah. I think it is a good point, and it's a gradual process. I would think that the logical progression of things from the development of this workgroup will lead to that. Are there, is part of their scope to highlight in fact, you know, greater than 10 for Psychosine? No. Not that I'm aware of at this moment in time.

I think we want to be able to demonstrate not only the value of higher tier testing, address barriers for state newborn screening programs, but to be able to just highlight exactly where you can get these tests, you know, as you improve, you know, your testing capabilities and programs. Maybe that will fall later on,

you know, in the coming months.

NED CALONGE: Christine?

CHRISTINE DORLEY: Christine Dorley, Committee member. So Jelili, I just had a question. As a proponent of second tier because we have adopted a couple in the Tennessee laboratory, I was just wondering with second tier testing sometimes when you're testing, you're actually finding a diagnostic marker. And I think about CAH and steroid profiling so to speak.

So my question was how is this Committee, which I am part of it, but how do we balance screening, which is not diagnostic in some of these second tier tests, which may be a diagnosis? How do we balance that? And it leads me to thinking about the definition of newborn screening because if we are doing a second tier that has a pathognomonic marker that we're identifying, and it helps, and it is diagnostic, this may be where we need to broaden that definition of newborn screening.

I don't know, but the thought about this is also maybe why some states are a little bit hard pressed to add a second-tier assay because of that definition that is now kind of shady as to what newborn screening actually is. Any thoughts on that?

JELILI OJODU: You mean the shady definition. I think it's true. No, I agree with you. It goes to everything that we talk about here when we talk about developing a case definition to be able to now and focus on what we're addressing, a condition or otherwise, but I think we need to highlight and demonstrate the utility and the effectiveness, and the reason why higher tier

testing is important in newborn screening first.

Other, it's almost like the core conditions and the secondary targets, and the incidental findings, and all of that fun stuff, which is on my next slide for counting conditions. I mean we will address that when we get to that point. And you know, three or four months down into this path, we have to be able to demonstrate again tangible, reachable goals.

You know, if this, as your Committee member comes up as something that is important that we need to be able to address because this is a reasonable barrier that some states are not bringing this on, then we'll develop those talking points, and then figure out how to market it.

But again, we've been doing second tier testing, or higher tier screening for a while. You know, some of the reasons that we're talking about here should be straight forward, and I'll stop there.

CHRISTINE DORLEY: I just want to make another point that the reason for higher tier testing is because we have we have inadequate first tier testing that produces tons of false positives, so you don't get a clear picture of who actually needs to be followed up, so I think it goes back to those vendors of these test kits that we are using to maybe hone in on deciding on better markers. That's just my opinion.

And you know, if that was to be done, and you could actually, you know, tell a true positive from something that is true negative, then we wouldn’t need higher tier testing.

JELILI OJODU: Yeah, from your mouth to God's ears, I think there are a number of folks that will say the same thing. Obviously, if we had a better first tier test we wouldn't need this, but we don't. And maybe that's another subcommittee that then addresses how we can have better first tier tests, but that's for another discussion, Dr. Dorley.

NED CALONGE: Cindy?

CYNTHIA POWELL: Cindy Powell, ACMG Org Rep. In addition to considerations that have already been mentioned regarding the higher tier testing, I appreciate what APHL is doing to address this issue. One thing as when the higher tier testing is taken out of the newborn screening program, and put into clinical care, we're often faced with--especially when those tests involve genetic types of testing, is that you know, we can't get coverage of it through, you know, Medicaid, especially with privatization of Medicaid coverage and private insurance companies.

So as a clinician, we can be faced with having to tell a family that, you know, your child has a condition that's been picked up through newborn screening, but we're not going to be able to tell you what it is due to, you know, an inability to get that paid for, so just another important consideration. I do believe that it should be part of newborn screening, not that the laboratories have to be doing all these additional tests, but just that there be some standard about, you know, to make sure it gets covered. Thanks.

JELILI OJODU: Thank you. And I agree with you 100 percent, Dr. Powell. This goes to the health equity aspect of it as well, and a number of folks have mentioned that in fact it will be helpful to just do molecular testing for hemoglobinopathies in the newborn screening arena before it gets to, as to what you just described there, so that every newborn will have the same kind of access to this kind of testing because that's not the case, but to be continued.

NED CALONGE: Jennifer?

JENNIFER KWON: So just quickly, I had wanted to ask Dr. Dorley what is the concern that she had about screening versus diagnostic testing because of course the SMA newborn screening test is really a diagnostic test. We call it a screening test. We always send confirmatory testing to, you know, confirm the result and the accuracy of the patient.

But, you know, it's a pretty--it's pretty much a diagnostic test.

CHRISTINE DORLEY: So, my response as I mentioned before, I am a proponent of second tier testing. For Tennessee, we send out for the copy number. And I do realize the seriousness of getting that diagnosis, and knowing what the copy number is because that helps with the treatment aspect of it. So I'm not against second tier testing at all.

My message, or my question is that there are so many labs that do not venture into that realm of second tier testing, even though there are a lot of false positives that are reported,

and from studies and discussions it overwhelms the newborn screening follow-up system.

But where is that fine line? How do you define newborn screening versus the diagnostic portion because a newborn screening laboratory is not a diagnostic lab? And so those lines are blurred, and that's why I was thinking there needs to be a broader definition of what newborn screening actually is because we're entering into the realm of helping to diagnose a baby.

JENNIFER KWON: Thank you.

NED CALONGE: Debbie?

DEBRA FREEDENBERG: Yeah, so actually I'm following on both Jennifer's and Christine's comments, AAP Organizational Rep. So really the question is that as more molecular diagnostics are coming onboard as they say, the line is getting blurred between diagnosis and screening. Is there any thoughts about including some sort of workgroup related to the molecular diagnostics, and not necessarily the technical aspect, because I know that exists, but how that interfaces with the follow-up and clinical care.

Because when you get your molecular diagnostics, you pretty much know your answer, even though you say you're screening until people repeat. And so I was wondering if there had been any thought about addressing that aspect of things?

JELILI OJODU: Not at the moment, but duly noted.

NED CALONGE: Okay. Condition naming and counting.

JELILI OJODU: Thank you, Dr. Calonge. So, the background here is that fortunately we call and name different

conditions different things across the system. There is a lack of harmonization of what--I mean not just what you see on newborn screening panels, but how we call the nomenclature around the conditions, and how those conditions are counted.

And I think this has been brought up to your attention quite a number of times, including our Org Rep. Dr. Tanksley highlighting this, and she's one of the two Committee Chairs as it relates to this particular workgroup. But why here, and I hear this from time to time is that why does it matter?

This is something that we need to articulate a little bit better, but why does it matter that a state states that they screen for 70 conditions, and another state say that they screen for 33 conditions? And it becomes so, I mean, it's complex as it is already, but the dynamics around that, and knowing in fact that there aren't that many, the differences between the 70 and the 33 when you actually look at it objectively is, in fact, that they are more harmonized than they look.

The implications is also political, but I'm not going to get into that right now, but over the last several years APHL listened to our membership, developed the framework for standardizing counting conditions, represented 17 members across the newborn screening system, but it also involves something that Dr. Dorley said a minute ago. What is our main objective in newborn screening, the screening part and this blur as noted when it comes to diagnosing or diagnostic testing?

As part of that work group and activities, I think we

came to a conclusion, and we've worked on a number of things, including the development of the definition of screening. Late last year the Advisory Committee, this Advisory Committee, thought that it was going to be important, not only to figure out how we can better harmonize what we call conditions, but how we count conditions, and so this is the second ad hoc workgroup.

Again, the only difference between the two years ago and now, moving forward, is that we have folks from the newborn screening system as noted here, as well as Advisory Committee members. Again, and once we--the idea is that everything that we develop as part of the workgroup will come to you all as part of suggestions, that you then take and move forward, and in helping address reporting and recommendations, or potential recommendations for the newborn screening system.

But the desired effect is for some kind of national standardized understandable, not only nomenclature, but way of counting conditions. And we can stop at RUSP and say count the number of core RUSP conditions, but again, when you go and look at different websites, even defining what those core recommended in screening panel conditions are, are different between municipalities.

Again, under the guidance of Dr. Tanksley they have met monthly since 2021. That work has continued with the revised scope of addressing not only counting but figuring out a standard language for each particular condition. The talking points I noted here is that we need to better articulate why we need to

harmonize counting conditions.

And there will be pushback. I heard Dr. Calonge noted earlier that we have no way of taking anything off, whether it's a condition that's been added to the RUSP, or other kinds of recommendations here. And so, once these conditions or disorders are added, it becomes pretty much becomes the gospel, and something that states almost always have to do.

The idea is then to present the suggestions to the Advisory Committee for some kind of national endorsement, but the suggestions will also come with how we plan to market all of this.

And I think that's going to be one of the toughest aspects of counting or naming conditions in that it's not just the laboratorians or the clinicians that we're talking about, but the families, and better understanding when we define what is on the core recommended uniform screening panel, and other things that we pick up as part of testing for that core, should those secondary targets or conditions be added, and be counted, so more on that later.

These are just the next activities that they're going to embark on. They will be able to meet in-person. There is and are some discrepancies in just the information that is on that original foundational paper from HRSA / ACMG report from 2006, and then on the website that we would love to be able to suggest some ways to be able to move forward, better align our activities.

There are folks who would just love to be able to just not highlight the secondary conditions that we have right now

because of the confusions around it, and then get the word out. I talked quite a bit about implementation and communication and marketing, but we're going to work on a dissemination plan, so at the Committee discussions.

NED CALONGE: Thanks for taking on this difficult, but important topic.

JELILI OJODU: Dr. Tanksley, did I miss anything in that highlight there?

SUSAN TANKSLEY: I think you have it covered unless someone has questions.

NED CALONGE: Ash?

ASHUTOSH LAL: I hope if you can clarify when you say secondary condition counting, and I understand this isn't ready for in-depth discussion, but are we talking about secondary conditions after the second tier testing has been completed, or is it just based on the primary?

JELILI OJODU: So, let's just use hemoglobinopathy as an example. I think there are different ways that states are counting that. On the recommended uniform screening panel there is the presence of S, C and I think Beta Thalassemia. And then that's on the recommended uniform screening panel. On the secondary condition, not targets, but it's interchangeable depending upon where you look.

There are other hemoglobinopathy variants, and it's just listed as that. There are folks that count each and every one of those hemoglobinopathy variants as part of what they test

for, or a part of the conditions that they add. And I think the idea is just to better either understand, and then in a nice way say that this is we're looking for the conditions on the RUSP, and the other conditions that we find as part of a secondary condition or a target are important, but they should not be counted.

At least that's my impression of some of those activities that they're talking about in moving forward.

ASHUTOSH LAL: Sorry. I understand that part. My question is if the conditions are being picked up on primary screen, and they're not taken for second tier testing, or higher-level testing for confirmation, the secondary conditions. Or are we talking about the secondary condition counting after the higher tier testing has been completed? So that's the if you say if you had a variant in your first tier, or first tier screen, would that be same for molecular confirmation if the state was part of doing that?

JELILI OJODU: Yes. That would be. But should that be counted as a condition that the state is screening for? I think-- did you want to add some thoughts there?

SUSAN TANKSLEY: I think you answered it Jelili. But essentially, we are trying to determine when a state should count for the purpose of saying my newborn screening program is screening for 33 conditions, whether hemoglobinopathies, is that counted right now on the recommended, on the core panel, there are three, so right now that would count as three.

But it sometimes is counted as three, sometimes counted

as four because of the on the secondary it's the other hemoglobinopathies, or maybe it's counted as 13. Just, so we are trying to come up with guidelines that states would utilize literally when you're talking about what are we screening for. It doesn't mean that it wouldn't go to second tier testing.

So, there's what you're screening for, and then there's how many cases you identify. Those are two different questions, and we are trying to focus on the first one, and that information would then later feed into how you actually count the cases that you identify. Does that make sense?

JELILI OJODU: Thank you Dr. Tanksley.

NED CALONGE: Natasha?

NATASHA BONHOMME: Hi, Natasha Bonhomme, Genetic Alliance. Thank you for the presentation. So far all of it has been really great, and particularly this last piece, which is something that you and I have talked about for almost the better part of almost two decades.

I guess a question I have is you know, I saw the information about the tool kit and the marketing and getting the information out to families and advocacy groups. But you know, in my experience, in the experience through Expecting Health, you know, whether it was Baby's First Test, or when we did the initial build for the NBSIC, the biggest questions come from state programs themselves.

You know, it isn't advocacy groups pushing for one name, or one count over another. It tends to be from within your

membership, or within the APHL membership. So, could you just speak to a little bit more what are the efforts going to be to have when this process is complete, states actually do that adoption, or I don't want to go as far as to use a word like adherence, but you know, that's really where it's going to start because so often the websites that you mentioned are only reflecting the information that's given to them from programs, so that would be helpful. Thank you.

JELILI OJODU: That's a great question, and I'm not sure if I have the time to be able to go through all of the thoughts because we haven't developed them yet. I will say though that the buying aspect, especially from member laboratories, is going to be crucial. You noted it quite well that in fact it's the states and this effort. This is part of the why and understanding is the juice worth the squeeze, as one of my colleagues will say time and time and again.

That, is it worth the effort to do this if states are not adopting this new paradigm shift, or whatever we come up with as part of this? Natasha, I think we're still in the early processes of better understanding how we're going to be able to not only inform but move the needle in this topic. But if you have any ideas, certainly I would love to be able to incorporate that.

And as part of our updates to the Advisory Committee we'll certainly be bringing the progress of our activities in moving forward. But yes, thank you for bringing that up, and it

will be an interesting--it will be interesting for us as we move forward. So I don't think there's any other hands here, so I'll quickly run through this.

And I think I'm a little bit out of time, but if not I'm just going to quickly run over the last slide. As part of newborn screening, it's important to understand and note where we are at the state of the states. I have the opportunity to give this quick overview for another meeting, not too long ago.

That in fact there are programs, and I know that we like to highlight the fact that there are 53 programs, or 56 programs, and each one does things differently. But I would stand in front of you, I am standing in front of you, and I will say that there is more harmonization in states than, you know, the lack of standardizations.

That there are 36 newborn screening programs, that not all states have a laboratory that they use for testing, that they outsource the testing to another state public health lab for all kinds of reasons, or a commercial entity, that almost not every state has a follow-up program, and in fact that what I highlighted early it came through HRSA's funding that 17 states are reporting some form of long-term follow-up.

Again, we need to figure out what that definition is, and what they're talking about, but we'll come back and tell you that later. And they don't just have to outsource to a state public health lab, they can outsource to a commercial entity as seven state programs do.

That states either test their samples for the most part, that there's a mandate to screen, a required one screen or two screen. The first screen 24 to 48 hours, or somewhere around there, and then that second screen for those states that are highlighted on this slide, there is a mandate to do a second screen 10 to 14 days out, and there's been a number of reasons why states are justifying this, but mostly it's to be able to pick up a number of underpinned conditions that they believe that those will be missed if they only do one screening.

This is the state of the states as it relates to the newborn screening and how states are screening. States and territories, not only all of the states, but the territories as well. And we almost always focus on the recommended uniform screening panel.

If you want to know if a state is screening for conditions that are outside the recommended uniform screening panel, you can find that information on our website, NewSTEPs.org. But we love to be, just for harmonization purposes, it's important that we use, and I strongly believe this, that the core panel is that N that we use here, and this is where we are for that.

I don't need to highlight this other than the conditions, the last condition that was added was GAMT. And this is just another way of showing that states are screening between 31 and 37 recommended newborn screening panels. I think there was a lot of discussion about--I know that there was a lot of

discussion about the public health system impact.

How long does it take? What is the feasibility and readiness of adding the conditions? How have we done the last number of conditions that we've screened for? We wrote a paper about this. We continue to collect information about this. As you can see here the average number of years to implement a condition after it's been added to the RUSP, you know, the longest right now seems to be Pompe, but it is--it ranges from between 2.2 years, and 4.8 years.

And again, we're able to screen, bring on SMA faster because of the implementation and the development of molecular technologies as a first tier for SCID, and that's where you see the differences here, but we continue to collect this information, and use it to make informed decisions.

That states charge different amounts for newborn screening. For the most part it's a fee for service. There are states that don't have a fee, but it's part of their general fund. That the average, the most number of states average about, you know, charge $100.00 to $150.00, and because of some of the states that are bringing on other conditions that are not on RUSP in particular, cCMV on that we are actually some of these states are charging about $200.00.

That 20% of states are not open six days a week at least. Most states are open six days a week, and then approximately 25% of states are open every single day of the week. I think this is important, especially when we continuously find

ways to be able to make sure that that newborn, whenever that baby is born, regardless of whatever holiday is embedded in between any one of those days can get that test, and report that result out as a recommendation from you all, for time critical conditions within five days, and then all of the conditions within seven days.

And then finally, I think this is my last slide, and I'm not going to spend too much time on the second and third bullet, other than to highlight some of the things that have been said. To Dr. McCandless' point earlier, I think it will be very important to hear from state newborn screening programs, as well as other federal entities, as the effects of the new FDA regulations on, and the impact of that on newborn screening programs.

I do believe that there is going to be--there will be a major shift that is going to affect our thinking, and the way that we do things here, but more on that later. That newborn screening is almost always still either in the news for different reasons, whether in these two cases the residue dry blood spots, so it was interesting to hear the discussion earlier about N equals to one, which I believe that that is very important as we move forward.

But to do retrospective studies on specimens that are not available because of these lawsuits, and there are more and more states that are destroying their spots and not the availability of spots to be able to do any kind of potential lab developed tests, or any tests, dwindles by the day, is something that is going to affect all of us.

And so, it starts with the residual dry blood spots, but it's now getting into the fact should newborn screening be done? And more on that later. And then the symposium. We do have a symposium coming up, so it's important to highlight that. It's in October. I hope you submitted abstracts, and we'd love to be able to keep the conversation going. I really do appreciate the time to be able to share that with you all today.

NED CALONGE: Thanks Jelili. We are so appreciative of the partnership with APHL, and I think everyone that missed your introduction knows that you're the Director for Newborn Screening and the Genetics Program at APHL. And also appreciate your work as Director for the National Center for NBS Excel, great work, and we always like having you here and keeping us updated, thank you so much.

JELILI OJODU: Absolutely, thank you.

(Applause)

LETICIA MANNING: And I just want to remind Committee members that more information on the lab FDA tests can be found in your briefing book. There is a website with updated information, webinars, that kind of thing.

NED CALONGE: Before we get to new business, I wanted to quickly clarify something I said yesterday. Shawn McCandless finished four years of working with the Committee, which is all you can serve. However, Jennifer and Chanika had some additional time because they didn't start right when they would have started, and that's what the extension, which was granted by the Secretary

was for.

Not because they are so much better, and less problematic than Dr McCandless, so I wanted to make sure folks knew that, and we appreciate that you're staying on for your full four years, that's great. Let me see, Michele, did you have any new business items?

MICHELE CAGGANA: Actually, another one came to mind in the discussion. But with the sunsetting of the regional networks, as we heard about earlier, one thing that was impacted was the ability to be able to create and also revise the existing ACT sheets for newborn screening, and other conditions as well, other genetic conditions.

So, that lost funding with the sunsetting of the networks. So I was wondering if this Committee could find a way to alert the Secretary about the redirections of funding from the network to the Propel and Co-Propel that we heard about, so that we can figure out a path that would allow either ACMG, or another organization to continue and revise this important tool is used quite a bit by the newborn screening community.

And I think the other, if we can make a recommendation that any new condition that's added to the panel come with an ACT sheet, so that was number one. And then the other item that came up was while Jelili was talking earlier was a discussion of timeliness, because as we're adding the second tier tests, things are just going to take longer, and we're not going to be able to meet these time critical guidelines that were established years

ago, which Susan and I talked about a long time ago, when this all started, so that's my two things.

NED CALONGE: Jeff?

JEFF BROSCO: Yes, thank you for that. We recognize the value of the ACT sheets, and before I think you recommended, we talk to the Secretary before we go there.

MICHELE CAGGANA: Yeah.

JEFF BROSCO: HRSA is already thinking about ways that we might be able to do this.

MICHELE CAGGANA: Good.

JEFF BROSCO: We'll get back.

NED CALONGE: And failing that you'll bring it up. Thank you. Cindy?

CYNTHIA POWELL: Yeah. Cindy Powell, ACMG Org Rep. Just regarding the ACT sheets, and thanks for bringing this up, Michele. The ACMG has been doing these, you know, expert members of the college volunteer their time to put together the ACT sheets and review them and approve them.

It has been, you know, funded. The infrastructure funded through the coordinating center grant. We are still hoping to continue that, but currently my understanding is that the ACMG Foundation, so you know, part of our organization that can accept donations, is trying to get some commercial funding to do this without causing any conflicts of interest in development of them.

But anyway, I appreciate, we appreciate anything that the Committee and HRSA might be able to do because these are very

important, I think, to our primary care providers. You know, they're utilized by states that when there is a positive screening, something that can be faxed to the provider who wants to know, you know, what do I do next? What do I tell the family?

And so these are really critical pieces of information. Thanks.

NED CALONGE: Thanks Cindy. Melissa?

MELISSA PARISI: Melissa Parisi, NIH. I just wanted to make an announcement about a funding opportunity for this community, and this is the Rare Disease Clinical Research Consortia. So, the NIH has 11 different institution centers that are partnering together with NCATS, the translational sciences center to put together multi-site consortia that study natural history rare diseases, also try to prepare for clinical trial readiness, sometimes early therapeutic development.

So all of these things that are so important for the rare diseases that are screened for under newborn screening programs. And NICHD, which is the Child Health Institute that I represent, we have sunsetted our newborn screening translational research network, or NBSTRN, with the hopes that we can put that money that we had set aside for that entity into more rare disease consortia, that would be focusing on newborn screening conditions.

And so, we're really looking for applications for groups that are interested in putting in applications for either conditions that are currently on the RUSP, or things with the potential to be added to the RUSP, and we'd be happy to talk to

you all if you're interested in putting in a proposal.

There are going to be two informational webinars coming up on May 22 and June 3rd. The deadline for the actual applications is August 13th, and please reach out to myself or Mollie Minier, and we would be happy to talk to you. Thank you.

NED CALONGE: Thanks Melissa. Shawn?

SHAWN MCCANDLESS: Shawn McCandless, Committee member. Thank you. I actually want to follow up on Michele's comment about the timing of this issue, and see where does that discussion stand? Is there a workgroup working on sort of redefining, or beefing up the discussion about the timeliness of results?

Because I think that as I recall this came about in a somewhat ad hoc way in the past, and has not been sort of formally readdressed to the best of my knowledge, and I think to Michele's very good point with some of the newer things that we're adding it's really going to become critical because of the second tier testing, and the delays that that imposes.

NED CALONGE: Jelili?

JELILI OJODU: Jelili APHL, APHL is actually addressing the next steps to timeliness here, and if it's okay I would like to introduce Amy Gaviglio, who most of you know, who could talk more about this.

AMY GAVIGLIO: Do I have permission to speak?

NED CALONGE: You do.

AMYGAVIGLIO: All right. Thank you. No. We do have a, as part of the new disorder subcommittee, we do have a small

task force that we've put together, including Dr. Berry as an SIMD rep, who was kind of one of the original foundations of the timeliness to think about the time criticality of these new diseases, and how they may intersect with tier testing.

We may come with some ideas or recommendations in terms of how we think about timeliness and its intersection of higher tiered testing, just so that we're not setting up essentially unachievable goals for programs, so we are working on that through APHL's new disorders subcommittee. Thank you.

NED CALONGE: So we'll hear more, thanks. I want to spend just a real quick moment recognizing how much work goes into each one of these meetings, and recognize the side row of professionals that make sure that we get this done, so starting with Tina and then Debbie, Alisha, Kim, and the staff who provide all the great technical work, and can type real time in front of lots and lots of people.

We appreciate everything you do to make this successful, and I think every one of the Committee members recognizes the time and effort you put in, so thanks so much. Our next meeting is August 8 and 9th, what a terrible time to come to Rockville, but we will be here in the heat and humidity, loving every minute.

Thank you everyone for your time, and I'm going to adjourn the meeting, thank you.

(Applause).

Adjourn

(Whereupon the Advisory Committee on Heritable Disorders in Newborns and Children adjourned at 2:05 p.m.)