THE ADVISORY COMMITTEE ON HERITABLE DISORDERS IN NEWBORNS AND CHILDREN

IN-PERSON/WEBINAR

HRSA HEADQUARTERS 5600 FISHERS LANE

ROCKVILLE, MARYLAND 20852 (Pavilion)

Friday November 3, 2023

9:30 a.m.

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COMMITTEE MEMBERS

Ned Calonge, MD, MPH (Chairperson)
Associate Dean for Public Health Practice
Colorado School of Public Health

Michele Caggana, ScD, FACMG
Deputy Director, Division of Genetics
New York Department of Health

Jannine D. Cody, PhD
Professor, Department of Pediatrics
Director, Chromosome 18 Clinical Research Center
Founder and President
The Chromosome 18 Registry & Research Society

M. Christine Dorley, PhD, MS
Assistant Director, Laboratory Services
Tennessee Department of Health

COMMITTEE MEMBERS
(continued)

Jennifer M. Kwon, MD, MPH, FAAN
Director, Pediatric Neuromuscular Program
American Family Children’s Hospital
Professor of Child Neurology
University of Wisconsin School of Medicine

Ashutosh Lal, MD
Professor of Clinical Pediatrics
University of California San Francisco
UCSF) School of Medicine
UCSF Benioff Children’s Hospital

Shawn E. McCandless, MD
Professor, Department of Pediatrics
Head, Section of Genetics and Metabolism
University of Colorado Anschutz Medical Campus
Children's Hospital Colorado

COMMITTEE MEMBERS
(continued)

Chanika Phornphutkul, MD, FACMG
Professor of Pediatrics and Pathology and Laboratory Medicine and Genetics
Director, Division of Human Genetics
Department of Pediatrics
Brown University
Hasbro Children's Hospital / Rhode Island Hospital

EX – OFFICIO MEMBERS

Agency for Healthcare Research & Quality
Kamila B. Mistry, PhD, MPH
Senior Advisor
Child Health and Quality Improvement

Centers for Disease Control & Prevention
Carla Cuthbert, PhD
Chief, Newborn Screening and Molecular Biology Branch
Division of Laboratory Sciences
National Center for Environmental Health

EX - OFFICIO MEMBERS
(continued)

Food & Drug Administration

Paula Caposino, PhD

Acting Deputy Director, Division of Chemistry and Toxicology Devices

Office of In Vitro Diagnostics

Health Resources & Services Administration

Michael Warren, MD, MPH, FAAP

Associate Administrator

Maternal and Child Health Bureau

National Institutes of Health

Diana W. Bianchi, MD

Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development

ACTING DESIGNATED FEDERAL OFFICIAL

CDR Leticia Manning, MPH

Health Resources and Services Administration

Genetic Services Branch

Maternal and Child Health Bureau

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Robert Ostrander, MD

Valley View Family Practice

American Academy of Pediatrics

Debra Freedenberg, MD, PhD

Medical Director, Newborn Screening and Genetics, Community Health Improvement Texas Department of State Health Services

American College of Medical Genetics & Genomics

Cynthia Powell, PhD, FACMG, FAAP

Professor of Pediatrics and Genetics

Director, Medical Genetics Residency Program

Pediatric Genetics and Metabolism

The University of North Carolina at Chapel Hill

American College of Obstetricians & Gynecologists

Steven J. Ralston, MD, MPH

Chair, OB/GYN Pennsylvania Hospital

ORGANIZATIONAL REPRESENTATIVES
(continued)

Association of Maternal & Child Health Programs
Karin Downs, RN, MPH
Maternal and Child Health Director (retired)
Massachusetts Department of Public Health

Association of Public Health Laboratories
Susan M. Tanksley, PhD
Manager, Laboratory Operations Unit
Texas Department of State Health Services

Association of State & Territorial Health Officials
Scott M. Shone, Ph.D., HCLD(ABB)
Director
North Carolina State Laboratory of Public Health

ORGANIZATIONAL REPRESENTATIVES
(continued)

Association of Women's Health, Obstetric and Neonatal Nurses
Shakira Henderson, PhD, DNP, MS, MPH, RNCNIC, IBCLC
Health Board Director
Vice President, Research Officer
University of North Carolina Health

Child Neurology Society
Margie Ream, MD, PhD
Associate Professor
Director, Leukodystrophy Care Clinic
Director, Child Neurology Residency Program
Nationwide Children's Hospital, Division of Neurology

Department of Defense
Jacob Hogue, MD
Lieutenant Colonel, Medical Corps, US Army
Chief, Genetics, Madigan Army Medical Center

ORGANIZATIONAL REPRESENTATIVES
(continued)

Genetic Alliance

Natasha F. Bonhomme

Vice President of Strategic Development

March of Dimes

Siobhan Dolan, MD, MPH, MBA

Professor and Vice-Chair, Genetics and Geonomics

Department of Obstetrics, Gynecology, and

Reproductive Science

Icahn School of Medicine at Mount Sinai

National Society of Genetic Counselors

Cate Walsh Vockley, MS, LCGC

Senior Genetic Counselor

Division of Medical Genetics

UPMC Children’s Hospital of Pittsburgh

ORGANIZATIONAL REPRESENTATIVES
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Society for Inherited Metabolic Disorders

Susan A. Berry, M.D.

Professor, Division of Genetics and Metabolism

Department of Pediatrics

University of Minnesota

P R O C E E D I N G S

Welcome and Roll Call

DR. CALONGE: Welcome back to day two of the Advisory Committee on Heritable Disorders in Newborns and Children meeting. I'm going to right away turn it over to Letitia for our roll call.

COMMANDER MANNING: Thank you. Good morning, everyone. I'm going to start with the Agency for Healthcare Research and Quality, Kamila Mistry? Michele Caggana?

DR. CAGGANA: Here.

COMMANDER MANNING: Carla from the Centers for Disease Control and Prevention, Carla Cuthbert?

DR. CUTHBERT: I'm here.

COMMANDER MANNING: Jannine Cody?

DR. CODY: I'm here.

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

DR. CAPOSINO: I'm here.

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

DR. BROSCO: Good morning.

COMMANDER MANNING: Dr. Michael Warren?

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

COMMANDER MANNING: Dr. Jennifer Kwon?
DR. KWON: I'm here.
COMMANDER MANNING: Ash Lal?
DR. LAL: Here.
COMMANDER MANNING: Shawn McCandless?
DR. MCCANDLESS: Here.
COMMANDER MANNING: From the National Institute of Health Mollie Manier?
DR. MANIER: Here.
COMMANDER MANNING: And Chanika Phornphutkul?
DR. PHORNPHUTKUL: I'm here.
COMMANDER MANNING: For the organizational representatives from the American Academy of Family Physicians, Robert Ostrander?
DR. OSTRANDER: Good morning.
COMMANDER MANNING: Good morning. From the American Academy of Pediatrics, Debra Freedenberg?
DR. FREEDENBERG: I'm here.
COMMANDER MANNING: From the American College of Medical Genetics, Cindy Powell?
DR. POWELL: Here.
COMMANDER MANNING: And from the American College of Obstetricians and Gynecologists, Steven Ralston? From the Association of Maternal and

Child Health Programs, Karin Downs?

DR. DOWNS: Here.

COMMANDER MANNING: From the Association of Public Health Laboratories, Susan Tanksley?

DR. TANKSLEY: I'm here.

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

DR. SHONE: Here.

COMMANDER MANNING: From the Association of Women's Health, Obstetric and Neonatal Nurses, Shakira Henderson. From the Child Neurology Society, Margie Ream? The Department of Defense, Colonel Jacob Hogue?

DR. HOGUE: Here.

COMMANDER MANNING: From the Genetic Alliance, Natasha Bonhomme?

MS. BONHOMME: Here.

COMMANDER MANNING: From the March of Dimes Siobhan Dolan?

DR. DOLAN: Here.

COMMANDER MANNING: From the National Society of Genetic Counselors, Cate Walsh Vockley?

DR. WALSH VOCKLEY: I'm here.

COMMANDER MANNING: And from the Society for Inherited Metabolic Disorders Sue Berry?

DR. BERRY: I'm here.

COMMANDER MANNING: I'm just going to remind folks of our conflict of interest requirements. Please note if you need to recuse yourself for any reason, if you feel like any parts of the conversation conflict with your role as an officer or a director or general partner, please reach out to me and let me know.

So the same rules as yesterday. Next slide please. As a reminder, meeting participation. All Committee meetings are open to the public. If the public wish to participate in the discussion or the procedures, it's published in the Federal Register, and announced at the opening of the meeting.

As you all know yesterday we had our public comments, and we also had listening sessions that were open to the public. Any further public participation will be solely at the discretion of the designated federal officer official.

For webinar instructions if you are having any technical difficulties please reach out to ekelly@lrg.org, and I'm turning it back over to you, Ned.

DR. CALONGE: Great. We can go through the slides maybe. Just a couple of quick items

from yesterday. I'll point out the agenda for today's meeting is going to focus on going over the updates from the listening groups that I think most of you attended or participated in yesterday, and again I thank you for your input and time.

As far as our conflict of interest policy, so we've taken the comments back and made revisions. I think as we talked to staff we felt we needed to probably go back to our legal advisers, which will also give us time to work out the way that we're going to approach organizational representatives and their conflict of interests assessments.

So, we're not going to have a vote on it today. We're uncertain because it's a bylaw issue whether the Committee needs to vote on it. That's one of the reasons we're taking this little pause, and we'll get back at the next meeting. On the other hand, we have completed answering questions about the expedited review process in the August 23rd meeting summary.

And those edits, I think, were forwarded to Committee members, and at this point I would entertain a motion to approve the minutes from a Committee member who needs to unmute.

DR. CAGGANA: I'll make a motion to

approve. This is Michele Caggana.

DR. CALONGE: Thank you, Michele.

DR. CAGGANA: Sure.

DR. CALONGE: Is there a second?

DR. CODY: I can second. This is Jannine Cody.

DR. CALONGE: Thank you. I appreciate it, Jannine. Will all Committee members please unmute and signify approval by saying aye?

CHORUS: Aye.

DR. CALONGE: Thank you. If there are any opposed you would unmute and say nay. Hearing none, the minutes are approved. Before we get to the listening sessions, I'd like to take a moment and see if Jelili Ojodu has any updates from the ad hoc groups that HRSA's NBS Excel program is hitting on : condition naming, secondary conditions, and second or higher tier testing.

Jelili are you with us? We're waiting for him to be promoted. It sounds so positive when you say it that way. So we're going to wait, Jelili hasn't joined us yet, so we'll probably do that a little later, and I'd like to move on to the report out for our groups. I'm going to start with the Public Health Group.

Listening Session Group Updates

Nomination Process

DR. CALONGE: And the way we thought we would do this is we would cover the questions on the nomination process, and then pause for a discussion, and then cover kind of the updates or the summaries for the second set of questions on benefits, harms and balance. So turning to the public health area, I'm going to introduce Shawn McCandless, Professor of Pediatrics, and the section head for genetics and metabolism at the University of Colorado Denver School of Medicine, and the Childrens Hospital Colorado.

His research is focused on newborn inborn errors of metabolism and Prader-Willi syndrome. He's currently the clinical team liaison and the site principal investigator for the Urea Cycle Disorders Consortium of the National Institutes of Health Rare Diseases Clinical Research Networks.

Joining him is Scott Shone, the Director of the North Carolina State Laboratory of Public Health. He is a board certified high complexity clinical laboratory director, trained in molecular microbiology and immunology. Dr. Shone is a member on the Clinical and Laboratory Standards Institute Expert Panel on Newborn Screening, a member of the

editorial board for the International Journal of Neonatal Screening, a member of the APHL Newborn Screening and Genetics and Public Health Committee, and of course, a previous Advisory Committee Member. Let me turn things over to Shawn and Scott.

DR. MCCANDLESS: Thank you, Dr. Calonge. I will start, and then at the end of each slide ask Scott to fill in some additional comments. Go to the next slide please. So we wanted to start with some overarching themes that came out of the discussion. And first and most important, was overall there was consensus that changes to the nomination process and system are needed.

And that led to a lot of discussion about how to further and better incorporate equity into the decision-making process. And there was also a lot of discussion about data collection and concerns about data collection specifically around who does it, who pays for it, and if there is a standardized package of data that is needed to move a nomination forward, that needs to be considered in the new process, so that we don't create new inequities for various groups that have fewer resources, or less resources, or where there's less, you know, pharmaceutical industry support for

developing the historical, you know, database of patient information.

It was important, there were concerns raised that whatever changes are made, we need to be careful that it doesn't further delay timelines, or add to the time that it takes to get it, a nomination, across the finish line. And there was some concern that having more centralized, a more centralized method of creating nominations might actually slow things down a little bit.

It's also possible that that could speed up the process, and members of the Public Health Group Listening Committee, or the people that were speaking thought it was really important to be cognizant of the potential for unintended consequences of changes.

This may go without saying, but needs to be said anyways. Go to the next slide please. Scott, I think let me finish up the overarching themes, Scott, and then I'll ask if you have anything else. Considering the purpose, there was a lot of discussion around what's currently in the nomination package that there is an expectation that there be at least one case identified by a pilot study of a population-based pilot study.

And the question that was raised was that

there needs to be careful consideration of why that is needed, and what is the information that will be obtained from that, and whether there may be a more efficient way for a particularly rare disease to obtain that information, and so that there should be a case by case review of that requirement to have at last one case identified by a population based pilot study.

There was some concern raised about balancing the benefit of newborn screening and early diagnosis for a specific disorder, or a specific group of disorders versus the risk of "breaking the system by the rapid addition of new conditions." And we'll come back to this later, that there is some concern that it's already becoming difficult as things are added at a fairly rapid pace that may or may not be multiplexed with other tests. That there may be straining of some state systems to add conditions within a three year timeline, which was sort of alluded to yesterday as what states typically say they can do, that may no longer be true.

There was some discussion among the group that it might be okay to create a more limited definition of what is newborn screening, particularly as it relates to the consideration of

clinical capacity to take care of the patients after they're identified and long-term follow-up, just to actually allow reasonable decision making.

And so the public health group thought there should be maybe a little bit more discussion around what is the definition of newborn screening that should be used when a new condition is being continued. And finally, the one overarching theme that came up over and over was that this newborn screening needs to be a continuous learning system that adapts to its learnings. Scott, anything to add to the overarching themes, and then we'll go to the nomination process?

DR. SHONE: I will say why don't you -- I think we're going to pause after the nomination process slide, for the others to talk about their nomination results, and I can share some thoughts after that slide if that's okay with you, Shawn?

DR. MCCANDLESS: Perfect. May I have the next slide please? So, specifically regarding the nomination process, there was sort of validation of the thought that there may be potential nominators who just don't have the bandwidth or resources to put together a nomination package in the current system, which is a major drive for change.

It's critically important to have a

mechanism for active involvement of active seekers, and those with lived experiences in any new process to make sure that their voice is both heard and amplified in the process. There was also some discussion around the idea of having a more clear definition of what does lived experience mean.

And there was some discussion about whether, you know, just what is the value of the importance of anecdotal stories, and a recognition that hearing individual stories is important, but needs to be -- that needs to be carefully worked into the framework of what the nomination process will look like to ensure that there's not -- that there's an appropriate balance between the heart-wrenching stories that we hear, and the evidence basis for moving a condition forward.

Although the group was very clear that it is important to hear those stories. That led to a discussion whether if there were a bundling of conditions, in other words if there were a group of conditions that were very similar that were going to be considered together would there be helpful to sort of bundle the family lived experiences information as well.

There was also some discussion around that fact that as heart-wrenching as the family

experiences are, and as important as it is to hear them, sometimes the agony and pain is very similar from one condition to the next in that while each condition is unique, and each family's personal journey and pain is unique, the broad themes of those stories are often very, very similar. And we wondered if there was a way to more efficiently capture that in the process.

There was a concern that implementation in three years is becoming more difficult for states, and that a rapid influx of new conditions that are not sort of simple add on's to existing assays would be -- could be very challenging, and could overwhelm newborn screening systems. Go to the next slide please.

DR. SHONE: So, I think so, I don't know HRSA, I don't know did you want us to stop at that nomination slide?

DR. CALONGE: Yes, they are. That's what we were told.

DR. SHONE: Okay. So, Shawn we're going to come back to the evidentiary review after everybody does nominations. I'll just add a couple quick thoughts. You know, I think in general, as Shawn said, our group, you know, why they graded the questions and the information solicited as part

of the nomination process, was correct, and generally on point.

But the process itself is where there was room for improvement. You know, the who's and how's of getting all that information submitted. And I want to reiterate the point that Shawn brought up around the concerns of centralization, particularly and potentially in a bureaucratic government organization of pulling together these things, and the potentiality for that actually contributing to delays and challenges, as opposed to making things easier.

So there was a recognition from those outside of government that everybody's bandwidth is taxed, and so what would be the resources that would come to bear if things were centralized, and that needed to be part of any kind of transition or change in the process of the nomination itself.

Also, as Shawn just highlighted, the importance of the different lived experienced voices, and if you centralize in a group that isn't directly connected with those families, would we actually end up losing the voices that we value? And so, that's why he spent some time I think on trying to sort out, you know, what's unique about the stories we hear, what's similar, and how do we

make sure we don't lose the uniqueness, but also grasping clearly what's similar across the shared family stories.

The learning system I want to acknowledge Beth Tarini's paper recently, where she talks about that as part of the newborn screening system conundrum that we're dealing with, and I would just like to just clarify on the lived experience slide, you know, I think one of the things we need to think about is there are many groups, and we heard that you have those who lived, who were identified through newborn screening, who were not identified through newborn screening, who may have had a false positive newborn screening, or who were identified due to sibling work.

And how much do we as a group want to weigh and balance all of those different lived experiences, and potentially others as part of the nomination process. So, thanks Shawn, for letting me chime in a couple of additional thoughts.

DR. MCCANDLESS: Thanks for those additions. So we'll stop here and let the team from, Ned and the team from HRSA lead us forward.

DR. CALONGE: Thanks so much, Shawn and Scott. I think now we're going to turn to the Family and Representative Organization Group, and

helping us with that will be Jannine Cody, Professor of Genetics and the Department of Pediatrics at University of Texas Health, San Antonio.

In 1985 her daughter, Elizabeth, was born with a rare chromosome abnormality called 18q minus. In 1990, Jannine founded the Chromosome 18 Registry and Research Society, as a way to bring affected families together, and to learn from each other. While pursuing her Ph.D. she developed a multi-disciplinary chromosome 18 clinical research center, the goal of which is to make the chromosome 18 conditions the first completely treatable chromosome abnormalities.

Joining her will be Siobhan Dolan, Professor and Vice Chair for Research in the Department of Gynecology and Women's Health at Albert Einstein College of Medicine, and Montefiore Medical Center in the Bronx. Dr. Dolan serves as a medical advisor to the March of Dimes, where she works to improve the health of babies by preventing birth defects, pre-term birth, and infant mortality.

And Jannine, I'll turn things over to you. And you're on mute.

DR. CODY: Sorry. Should have known

better. Thank you. And I -- we had a fabulous discussion that is I would say completely aligned with the report from Shawn and Scott. Can I see the first slide please? Or the next slide? And the families felt that the advocacy groups were in fact the best people to put together a nomination packet, sort of as a neutral territory, safe territory for researchers, laboratory, public health people to come together.

But as pointed out, they often don't have the resources, and it's not really just money that they don't have to support getting all this together, but it's the person power, and actually as pointed out by the public health group, the statistical expertise and just the components that are actually required in the nomination packet. And so, serious guidance from HRSA and help putting together a nomination packet, and just to know what exactly is needed and what is not needed, and how to focus those inquiries.

And so, of course, they're seeking partnership and collaboration regarding all of that sort of process getting the data collected. And very much every part of the discussion the whole way through, they really thought that the families would like to be involved earlier. They were

feeling like the family view is sort of an afterthought after the evidence-based review is done. And then you hear from the families. But the decisions are really made on the evidence-based review, and they wanted to have the family voices involved earlier, maybe even a part of the evidence based review. Now, I was going to start, and forgot to thank Donna Johnson, who did a great job facilitating the discussion.

We had a really positive and thoughtful discussion. Siobhon, do you have anything to add about the nomination process?

DR. DOLON: No. Thanks so much, Jannine, that's perfect.

DR. CODY: Okay. All right. Thank you.

DR. CALONGE: Thanks. Okay. We're going to turn now to the Laboratory Session, and helping us there will be Michele Caggana, who's the Deputy Director of the Division of Genetics, Chief of Laboratory of Human Genetics, and the Director of the Newborn Screening Program at the New York State Department of Health.

And she works closely with NICHD, CDC and HRSA as principle investigator on several ongoing grants and contracts. She is actively involved in several associations of public health laboratory

committees and subcommittees. Susan Tanksley, is the Deputy Director in the Laboratory Services section of the Texas Department of State Health Services in Austin, Texas.

She manages the day-to-day operations of Texas's public health laboratory. She chaired the APHL Newborn Screening and Genetics and Public Health Committee from 2011 to 2017, co-chaired the Newborn Screening Work Group for the Mountain States Genetics Regional Collaborative Center, from 2009 to 2015, and has been a long-time supporter and member of the Committee.

So at this point I'd like to turn things over to Michele.

DR. CAGGANA: Thank you. Good morning everybody. We had a good session yesterday. We were led by Loraine Swanson and put together a set of slides for you, and then Susan, you can chime in if you feel free, or I miss something. Next slide please.

Okay. So we thought an answer to the first question that really the idea of getting on the list was your foot in the door, and that that should be a bare bones approach. And maybe just as simple as naming what the condition is, what the newborn screening test is, and what the treatment

is. And potentially, obviously, availability of a diagnostic test.

And we felt that this would be a very simple way to decrease the burden on the folks that are nominating conditions for the panel. It improves accessibility, and it levels the playing field to allow people to get in the door.

We truly understand that we will need another step, and that will be as, I believe, public health, it's going to maybe add additional time on the front end that are going to require resources. We already gathered that information, but we felt allowing that process to start, and how conditions on a list would impact the timeline for evidence-review because the work will be done upfront, and that may impact the overall timeline.

Obviously, in order to be able to do this we're going to have to figure out who meets that interim step, and works to get together all of the information that's needed because at the end of the day we still need everything that's in the nomination package as it currently stands.

We talked about the fact there is already a list of candidate conditions. A lot of effort was put in by the NBSTRN and Jennifer Taylor was in our group, and that was about 34 conditions that

are already on that list, and essentially have gathered these bare bone pieces of information.

And we need independent stakeholder advocacy and federal agency input in order to be able to make this work in practice. Next slide please.

So in response to the second question, we again thought that if we lowered the intake for the nomination that it actually will remove those barriers for advocacy groups. It will also allow us to hear from groups that maybe we hadn't heard from in the past.

And we talked more about that in some of our later slides. And I agree with the family that we need a little bit more of a bidirectional dialogue with the stakeholders, and the parents and advocates because as was mentioned, most of the time it's sort of a one-way we hear from them at various aspects of the Committee meetings, but we really should incorporate some of their input early on as we develop the package as it goes forward.

And we need to ask for all the voices. We talked and spent a bit amount of time talking about the fact that, you know, we don't know what we don't know. We know who comes to the table, and we know what groups are known to us over a period of

years, and we really need to work hard to find those other folks that have input, and they just don't have the means, or a way, or even the knowledge to know that we want input from them.

And we also talked about the fact that we do hear a lot from families who are impacted by rare conditions, but we really would like to hear from families in general, so more of a focus group type approach, or something along those lines, so that we can sort of get the input from families in a balanced way.

And then we're sort of stuck with how we find them, how do we gather the information, and format the input into a nomination package more efficiently. And how do we get that balance, that sort of balance? And so we talked about do we hold listening sessions for those individuals? Do we do outreach via social media? Are there other ways to get those folks to the table as well?

And then the last set for this, we noticed that the whole term nomination package as it sits is daunting, and it sounds like an awful lot of work before anyone who picks it up and actually looks at what's in it, and what they would have to collect in order to nominate a condition.

And again, all of the information that has

to be gathered at some point, and we're still going to need it regardless of how it's assembled. And so, we feel that it was unlikely having this sort of low bar to get into -- onto the list, that implementation will go any faster, we still need extra time to work on that. And then who is going to own that?

And we spent a fair amount of time also talking to the effect that we need a reset. There's this idea that once it's on the RUSP, that's the end point for the Committee. And really, our metric for success is implementation. We get this feeling that once we get the letter from the Secretary, we should hit go, and then the maps will all come up and we'll see who's screening, who's not screening. But at the end of the day our goal for the laboratory perspective, is to actually screen the babies and implement the new test. And so we need a change in the mindset that RUSP is sort of our end, our end work.

So that was our input and Susan I'll let you comment.

DR. TANKSLEY: I don't have anything to add. Thanks Michele.

DR. CALONGE: All right. Nice presentation. Thank you. And great points in

addition to the ones we've heard so far. So the last group to go nomination, before some discussion is the group on Clinicians. Leading that is Jennifer Kwon, Professor of Neurology at the University of Wisconsin, School of Medicine and Public Health.

She's the Director of the Pediatric Neuromuscular Program at the American Family Children's Hospital. Dr. Kwon is trained in pediatric neurology, and neuromuscular disorders. Joining Dr. Kwon is Colonel Jacob Hogue, currently the Chief of Genetics at Madigan Army Medical Center, which is located on Joint Base Lewis-McChord in Takoma, Washington.

In this role he's responsible for the medical care of individuals of all ages with suspected or confirmed genetic conditions throughout the region. In addition to his role as a clinician and subject matter expert on genetics in the military, LTC Hogue currently serves as the Chief of the Department of Clinical Investigations, and the Chair of the Ethics Boards at Madigan. With that I'll turn things over to Jennifer, or to Dr. Hogue, one of you.

DR. HOGUE: Yeah, yeah, I think I'm actually going to do the first sections, so I'll

cover the nomination process discussion.

DR. CALONGE: That's perfect.

DR. HOGUE: And then Jennifer will cover the next section, so next slide. So, nice to hear individuals coming from different perspectives covering a lot of the same information, and I think having a lot of the same ideas about things, so I think a lot of what we're going to discuss mirrors what was discussed already, so next slide.

So, we agreed with the other groups that the importance of considering different ways of going about the nomination process, given the importance of ensuring that there is access to making a nomination to groups that don't have large support advocacy organizations that don't have large financial backing because it's a large burden, or the amount of work that is required for making a successful nomination. So, certainly open to options to make that more accessible.

The how that would happen is certainly a question. I think the other groups have talked about, and identifying whether that is within HRSA with our Committee, with another federal organization that would take on a component of that, knowing that there are other groups that already provide some support for that that are

external to this particular Committee that will help groups with that.

The other discussion that we had was thinking about whether there needs to be proactive identification mechanisms, whether that's internal to our Committee to saying is there a monitoring of new FDA approvals, new treatments that have been published where we should have some forward thinking of them reaching out to organizations to think about whether they're ready for a nomination packet, providing assistance to move their position along towards a nomination.

We also discussed the NBSTRN list, and whether that will be maintained, or how that will be maintained going forward, and as a resource to facilitate this type of proactive identification. We discussed a little bit about mechanisms for how a process would look differently, or how we could assist groups with making a nomination that may not have the larger resources.

We talked about assigning either a HRSA or ACHDNC member as a champion for nomination packages, with the recognition that some of this already occurs. It's a component that we don't necessarily see at the time of presentation. We also recognize, as the first group did, the barrier

of an identification through a pilot program of an individual with a disorder, and often is a large hurdle for a condition to get over to be successful and having a nomination package going forward.

And we discussed whether there was a way to facilitate through this Committee, a condition otherwise meeting requirements that hasn't had that yet, whether a nomination that comes through in that capacity that we could facilitate that leading to funding through a pilot program, recognizing that there are programs that are available and grant mechanisms to support pilot programs, but that those may have the same barriers for facilitating someone applying for those programs, as there may be for nomination packages. So we might be not recognizing conditions that don't have large organizations to support them. Next slide.

For the second question we did recognize that the current directives that we have for how to move forward for involvement of advocacy organizations has been valuable, and that the value of hearing those voices.

We also recognize that the public comment sections that we have are certainly they're a listening session more than a back-and-forth discussion, and discussed whether there was a value

to adding an extra component again that would expand that, that may be separate from the time period where we currently have that in place.

There was also some discussion of the value of in-person meetings, and that some of those discussions and the recognitions of where those lived experiences come through the breaks that in person meetings, or before and after at those meetings, and having these virtually takes that opportunity away, and that has an impact on individuals understanding of that. Next slide.

And then finally we again, we talked about the NBSTRN list, and the value of that, and how that will be maintained going forward, and knowing if there's other conditions that may be kind of near the line of being ready for nomination, and is there value to us having an idea of what's coming around the horizon.

Again, we talked about this recognition that particularly changed the nomination package process where more conditions could come in earlier, and there's a central need for work that goes along with that that they will be a need for expansion of either the Evidence Review Committee, or other components of what happens to take on that work as well.

And then we also discussed, you know, that again this learning process, and that we struggled with long-term follow-up for newborn screening conditions, and tracking that data going forward. And really having that information would actually inform us back at the beginning of what we're looking at the front end.

If we're looking at data for a new condition being nominated, and having some information about how that's been successful, or how that's not been in the long-term follow-up for other conditions in the way that we don't do a great job of capturing right now, would actually allow us to do a better job throughout the whole process.

And I think that's all I have. I would also just say that I think Mandy David did an excellent job being our facilitator as well. We had a great discussion, and I think she was a big part of that occurring the way that it did.

DR. CALONGE: Jennifer, did you have anything to add?

DR. KWON: I think Jacob went over everything really well. I thought the biggest theme as he said was people thinking that maybe HRSA and the Advisory Committee needed to be more

proactive. We needed to have a better sense of what was out there in terms of treatments, and disorders that would be likely to be treatable and plan for that.

Obviously, we recognize that the HRSA staff needs a lot of funding and support in order to do that. So I think those are the two big things.

DR. CALONGE: Well, Dr. Kwon and Colonel Hogue, thanks so much. That was excellent. I want to thank everyone again who participated in the listening sessions and provided input. I want to thank our presenters, and before we get to evidence of benefits and harms, I'd like to go ahead and have a discussion just on nomination.

Committee Discussion

DR. CALONGE: Again, we'll start with members of the Advisory Committee and follow-up with organizational reps, and I will open the floor.

And while people are formulating their thoughts for the PFAS consensus study, the National Academies of Science Engineering and Medicine did something they had not done before, which was hold three regional town halls to hear from people in

affected communities where water supplies had been contaminated with PFAS, which is a very specific long-lasting manufactured component that ends up being in water supplies, and then ends up in humans, and is associated with several diseases.

The listening sessions included presentations from local experts, so kind of subject matter experts, as well as talks by leaders in separate advocacy groups who had been working in this area for some time, and then a longer session of testimony from people who felt, who were sharing their lived experience about how they felt the exposure had manifested in them or their families.

It was unique because it was the first time the academies had reached out to scientists in a formal way, and it greatly informed the Committee as it went forward in considering its work in the consensus study. And so there was much more since the sessions were longer, there was much more opportunity for dialogue, questions and answers between committee members, and members of the public.

I think I'll just say that the leadership for the National Academies felt that this was a very valuable exercise, and they're now looking for how to include that when they have adequate

resources and further consensus studies going further.

So that's just something I would offer for HRSA and the Committee to think about as a way of deepening the outreach involvement and listening and evaluating the input of lived experience and families affected by the inborn errors, or the heritable disorders of newborns and children. Dr. Powell?

DR. POWELL: Thank you. Thank you to all of you for the presentations. You did a great job summarizing everything, at least I know from the group that I was involved in, which was the clinical group. I just wanted to give a little bit of historical information regarding something that Shawn brought up in the public health session about the requirement for having one case identified through prospective newborn screening.

And I'm not saying I advocate one way or the other for this, but it was done because, you know, as was discussed yesterday, you know, it's a newborn screening system. It's not just a laboratory, and for a laboratory to be able to detect like a case, or to do maybe anonymized dried blood spots to see if the assay works properly.

But it was really to see if in the real-

world setting, if one would you know, be able to detect a case, and then make sure that there was appropriate follow-up, and also to you know, look at what happens for false positive newborn screens. And the only other thing I wanted to mention, and I'm sorry I didn't say, Cindy Powell, organizational representative form ACMG.

The other thing was something I brought up yesterday in our session was, you know, perhaps to get more input from all of those patients, parents, advocates, others. You know, not only for those who have had a child with a condition under consideration, but also those who, you know, may have elected to not have a child treated, you know, where a condition has been detected, or gone through, you know, false positive newborn screening result was a consideration of having like a standing group of the public with, you know, experience and knowledge about newborn screening to start out with who could be brought in, you know, during the evidence-based review phase for conditions. Thank you.

DR. CALONGE: Thanks, Dr. Powell. Jennifer?

DR. KWON: So, I think that one of the -- so Cindy's comment was not forgotten, it

just made it into the discussion of the harms. But I think that along with HRSA's mission to be more proactive, and to have maybe a better sense of what's out there, I think that there needs to be, and I think part of what I've heard here and there, and maybe I tend to say it the most, is that we publicly need to be clear in what we're trying to accomplish with newborn screening. I think that one goal of newborn screening is to screen all babies who have treatable conditions, but I think that we sort of have to set some rules, and maybe we need to take a look at the landscape first before we set the rules.

But I think that there's been, there was also some discussion that came out that maybe we should consider ourselves a Committee for Heritable Disorders, and that approval for the RUSP is only one component of what we do on screening newborns, and judging which disorders are best to screen in newborns is one part.

Looking at the landscape of heritable conditions with treatments that may benefit from alternate ways of screening and diagnosis, maybe that's another consideration. And again, that's a big, it's sort of a big paradigm shift for HRSA, but it may be one way to think about the ever-

growing list of potentially treatable heritable disorders that are out there.

DR. CALONGE: Yeah. Thanks Jennifer, and this is not -- I think I first heard this form Michele Perrier. Maybe in 2010. And that they purposefully gave us this acronym that none of us could pronounce in a reasonable way because it wasn't the Newborn Screening Committee.

It's the Committee on Heritable Disorders in Newborns and Children, and we often miss that, the children part, and I think even Bob Ostrander yesterday sent me an email saying maybe we should look at, you know, heritable disorders, and think more broadly.

So the discussion and the comment is not new, and it's coming at a time whereas we're looking at new processes, trying to redefine how we can be more effective in terms of looking at the system and the RUSP, can we also be thinking more broadly about how to longer across the childhood spectrum, thinking about our role and what we should be doing and advocating for in other areas, so I appreciate that comment. Shawn?

DR. MCCANDLESS: I want to just echo that sentiment. I think it's really important as we've discussed before that we broaden our focus because

-- and that reflects one of the comments that came up that we'll be addressing. Scott and I will mention in the next few minutes, which is that currently it seems like newborn screening is seen as the tool to solve many problems with our healthcare system, and it just really isn't, and we need to reflect that.

But what we can do is we can reflect on when are appropriate times in the lifespan of a child or an adult, to screen for, particular for a child, to screen for conditions that are pertinent at that point in life.

Another issue that came up in the listening group for public health people that I want to circle back to is the potential for unintended consequences. And I dread unintended consequences of every decision we make. One that occurs to me that we could see here is if we're transitioning the mechanism, there could be some confusion about incoming nominations, so should we create some sort of clarity around sort of which guidelines, which matrix, which process is going to be used as nominations come in?

Should we consider even like as some other organizations have done, a brief pause on considering new nominations while we work out the

mechanisms for the decision matrix and the nomination process.

DR. CALONGE: Yes. I appreciate that comment. I've been wrestling with this in talking to HRSA about the fact that we continue to see nominations. We know people are excited about getting things in front of the Committee, and we're kind of designing the new car as we're driving it on the highway.

Experientially, I can tell you that never designs a good car. It may not even design a car that gets you to where you wanted to go. In trying to think about how to think about new nomination in a period of rapid change, reconsideration of decision making, even getting better community engagements on how we think about the balance of benefits, harms and helping HRSA decide how they might -- HRSA and CDC and NIH might be able to better support the nomination practice.

I do worry that the bandwidth of the Committee as a whole, and our ability to objectively look at conditions that are coming in now are loggerheads, and that we don't have the resources to do everything at once, and then to do it fairly. So I do think we have to come up with a solution. The issue about pausing I'll just say is

not new, so when I joined the Committee in 2009, we had added 29 conditions associated with aspect screening, and we didn't add anymore until we spent two years, and I'm not saying two years, but actually designing the evidence-based process that we're going to move forward.

When we hit a snag with cyanotic congenital heart disease because it was a point of service test, and public health didn't have the relationships with hospitals to implement that screening, we again took a pause. And didn't take any new nominations while we worked out the kind of public health assessment and we did the matrix.

I said we, I was just consulting at the time, so I can blame that on other people. But it's not unusual to say could we pause on new nominations say for a six-month period of time, and really work on these.

I think the other interesting timing piece is NASEM result, which is going to provide recommendations on how we should think about going forward. And so I think it is something that maybe after we get through the RUSP process, we discuss a little bit further as a Committee, so thanks for your comments. Ash?

DR. LAL: I was just thinking about there

have been several comments during the presentations about equitable access to the nomination process, and the fact that the nomination process ends in a vote, an up and down vote to proceed further, when in it's based on what's probably presented in the package itself. And if there is, just based on my experience in the past year, I wonder if there's enough information available to the nominators that shows that there are certain things that if they're not in place, or if there's information that's potentially lacking, that will reduce the likelihood that the nomination would get to the next stage.

So that brings us kind of back to is there a need for a pre-consultation before the nomination packet is submitted as a partnership, almost like a pre-review. That's almost like adding an extra step there. But that would help to potentially level out the field between those nomination packages that don't have enough resources and experience of doing this.

DR. CALONGE: Thanks, Ash. Go ahead.

DR. BROSCO: This is Jeff. Just to point out, Ash, that right now in the current process, HRSA staff are always available to people who have a nomination package, and there's often a lot of

back and forth to help nominators put their package together in the best way possible, so that's something we currently do.

DR. MCCANDLESS: Also, the Nomination Prioritization Subcommittee serves in that role as well, it sort of takes a review of the nomination, sends back question to the nominator, and suggestions.

DR. CALONGE: Thanks Shawn, Chanika?

DR. PHORNPHUTKUL: Thank you. I was pleased to hear that for a different group actually had the same concerns or thoughts about ensuring the equity and access. And I think this is something that perhaps HRSA and the team can come up with what's the mechanism for that.

I think the discussion we had with monitoring the FDA approval medications, and so on and so forth. So that's, you know, those are actually the groups that probably will likely be nominated. It's the other condition that as medical care continues to evolve, they have a better outcome based on, you know, other interventions.

So I think a neutral proactive nomination -- consideration of literature is going to be helpful to ensure equity for our patients.

Thank you.

DR. CALONGE: Thanks, Chanika. Shawn?

DR. MCCANDLESS: Just to respond to Chanika though. We shouldn't, I don't think we should just -- I don't think we should make the FDA approval of a new drug the major focus. If we did that we probably wouldn't have gotten, you know, guanidinoacetate methyltransferase deficiency added, because there was no new drug, there was no novel treatment, it was just old-fashioned dietary therapy and supplementation.

And we don't want to create a higher bar, or sort of make other conditions have to work harder. The other thing about monitoring FDA approved drugs is that it seems to be for a lot of these conditions, the drugs get approved based on very short follow-up periods, and we don't have always the natural history of the -- the new natural history of the treated condition to make a decision about something as important, and as broad-reaching as newborn screening.

So I would be hesitant to sort of create an expectation that as soon as an FDA drug, which you know, unfortunately is, as we heard yesterday, is there is currently an expectation that as soon as the FDA approves a drug, then that condition

automatically should be, you know, the next step is get newborn screening.

I fully understand that. I understand why that happens, and why people feel that way, but at the same time as an evidence-based group, we want to be really careful to make sure that we have the evidence of meaningful efficacy and long-term efficacy that we need before we make a decision, so maybe focusing just on new FDA approvals isn't the best way to go.

DR. PHORNPHUTKUL: Sorry. I didn't mean to come across that way. I actually meant that that's probably not the best way to go because that's actually the group that would actually have more resources and, you know, the ways to capture attention. I actually meant for I was really thinking about guarantees, so that was -- thank you for making that clarification.

DR. MCCANDLESS: I apologize for not listening carefully enough.

DR. CALONGE: Yeah, Chanika, because that's what I heard you say, so Jennifer?

DR. KWON: And just to follow-up on that, I think the other reason screening the FDA's sort of approval list came up was again these are things that we as a Committee should be aware of. I think

part of the background message that we're hearing in the nomination process is that as a Committee we tend to be reactive.

We react to the application that's in front of us, but there is a landscape of treatable conditions out there, and there seems to be a certain choreography to how advocates are presenting their case. So we are hearing about disorders in advance of what is likely to be FDA approval, in advance of a package coming through.

And all of that is good. I think it's great to be prepared, but you know, I think that to have some sense of what's out there, and what seems like you know, who we can support and how we can use this advanced information to help us use our time efficiently, and the HRSA staff time efficiently and effectively.

Also, what kind of funding support HRSA is going to need. If we have, you know, two to three dozen new disorders with treatments that are going to be out there, that's going to be, I think, a very new kind of Advisory Committee for Heritable Disorders that we'll need to be able to handle that. So, I think that's part of what I was hearing as well. When people were talking about considering the FDA in this.

DR. CALONGE: Thanks Jennifer. Okay. Last comment on this section is going to be from Natasha, hopefully brief, Nastasha, sorry.

MS. BONHOMME: That's okay. This is Natasha Bonhomme from Genetic Alliance. Can you hear me?

DR. CALONGE: Yes.

MS. BONHOMME: Okay. Sorry. I'm on my phone, so it's a little bit of a different layout. I just wanted to note that, you know, in some of the language that we are using, we are saying talking about the family perspectives, and family stories. But we're an evidence-based group.

And I really encourage us to use the word and because the family stories, and the perspective of families can be collected with methodology, and from an evidence-based approach to be able to fit if the resources were there for that to happen, and the infrastructure, which I believe is kind of the purpose of this discussion that we had yesterday and into today.

And that did come up quite a bit in the family work, breakout group, or sorry, I can't remember what we were calling that. So just to encourage that, you know, we hear the family stories. We know what advocates are thinking, but

we're evidence based to really say how do we move that knowledge into an evidence-based format that can then be integrated, whether nomination by nomination, or overall with this work. Thank you so much for the time.

DR. CALONGE: Thank you so much for that point, Natasha, and I think it's a critical one to kind of keep in mind. So we had a great discussion. I think there were some similarities. The issue about back and forth I was reminded that there are families, representatives, advocacy representatives on the evidence review groups.

Evidence-Based Review Process

DR. CALONGE: And with Natasha's comments, thinking again more purposefully about how to capture, and then quantify or quality, or bring in the perspective of families into the evidence flow is an important point. So I appreciate those comments, and I'm going to turn back to Shawn, to talk about benefits and harms and balance.

DR. MCCANDLESS: Thanks, Scott. Scott is actually going to go through our next set of slides. Thanks.

DR. SHONE: Right. Just waiting for the slides to come up. Sorry, Dr. Calonge, there was

no way I was going to remember what Shawn put on all these slides for me to read, so. Thanks. And thanks to Shawn. I'm going to try to cover the next three slides real quick, and then come to Shawn to wrap up for us in public health.

But when we went to the discussion of the evidence-based review process following the nomination process, you know, the main points of discussion were that it was important to look at the outcomes that parents and families care about, and not just the intervention and treatment itself.

That there was an agreement that, and we heard some presentations of the Advisory Committee about the benefits of early intervention. The benefit that there are other family benefits. The immediate family, as well as extended family that newborn screening can provide, and it is important for us to consider those beyond the traditional impact on the child who's being screened themselves.

We did have a lot of questions about how to measure and weigh those relative benefits, that net benefit and the balance of benefits and true harms. And particularly focused a little bit of time on true positives and false positives. We had a couple laboratorians on our public health group,

and so we inevitably strayed a little bit into Susan and Michele's domain a little bit, but it is important.

And it is an important part of the evidence-review process about the performance of the screening test, and its impact on outcomes. And the criticality of minimizing false positives and potentiality to look at multi-tiered testing approaches as part of enhancing the benefits, and reducing the harms as part of this process. Next slide.

Yeah, there was you know, this general question that I think we've struggled with is standardizing and potentially identifying a way to score the quality and magnitude of benefit. You know, it inevitably comes up. What's the difference between significant and moderate?

And there's inevitably a desire to try to standardize that with the understanding that newborn screening is not black and white. It is all the shades of those who we serve, and so I think that that's an interesting discussion that we need to sort out. Shawn mentioned this, Debra mentioned this, Shawn chimed in about the role of newborn screening in a larger context of the healthcare system.

We talked about this I think last year around implementation barriers, and that challenges with the healthcare system shouldn't be a factor, at least a major factor in adding a condition to the RUSP that otherwise meets all the criteria. And that part of the process would be to monitor and adapt to the trends in the healthcare system.

But we can't expect newborn screening to fix the problems of the healthcare system. As I said last year, we had a discussion that newborn screening exceptionalism doesn't solve all the issues of the medical system or the public health system, yet it overlaps both. And so we need to recognize that, and challenge all the other organization and all the other groups that we work with and partner with that there are needs of newborn screening within their systems to address.

And we basically need to follow the evidence, and the overarching goal of newborn screening, which is that early diagnosis impacts the outcomes. That is really the hallmark of newborn screening. Next slide please.

And so, you know, there's always a discussion of uncertainty, and where that falls into our evidence review, and how much weight does uncertainty hold. Uncertainty about the conditions

themselves, uncertainty about the outcomes of treatments, as Shawn mentioned earlier. The natural history of these disorders, even going into screening, isn't completely and well understood. And that newborn screening is going to completely change even what we understand. Often because it leads to the recognition of milder forms.

And so, we need to wrestle with what is our obligation to the children and families diagnosed with these milder subclinical forums when population screening is traditionally based on addressing and trying to ameliorate the most severe forms. And does uncertainty and gaps in data justify population screening to get the answers?

Historically, we've said no. That we have an obligation, but as diseases become more rare, and those conditions we consider are more rare and rare, and data becomes scarcer, how do we balance out our obligation to population screening with the need to identify data sources? And I think that this has become a widespread discussion in the newborn screening system.

And I think the next slide is our other thoughts, and I'm going to let Shawn wrap us up for public health.

DR. MCCANDLESS: Thanks Scott, and Scott,

thank you for that nice presentation. I know you -- Scott had to go to another meeting when we were making the slides, so he wasn't involved in the sausage making, so he did a great job of recalling the content and reflecting on it.

Just a few last thoughts was that in the need for data collection a thought that was raised was that there's a tremendous amount of data around genomic variants, and genetic variants. It's available in databases that are held by commercial or private laboratories, and that there would be a lot of, you know, there have literally been hundreds of thousands of exomes and genomes performed in the United States, if not millions.

And if that data were available to newborn screening systems, we would learn a lot about specific variants that would inform our ability to use genomic testing and genetic testing to enhance newborn screening. Mei Baker brought up a point, and used the term next gen newborn screening to reflect the fact that we're getting away from just measuring phenylalanine or measuring T-4 or TSH in newborn screening.

And that we need to embrace our ability to use algorithmic data to combine different datapoints to look at follow-up, to follow trends

in the healthcare system, and that we really need to be cognizant of the fact that newborn screening, we need to keep a broad focus and think about what could newborn screening be, rather than what has it been in the past, and how do we keep doing the same thing, only incrementally better.

And Mei, if I didn't capture that exactly, what you said correctly, I apologize for that. And then there was also some -- a fair amount of discussion about the need to reevaluate conditions on the RUSP, and Scott Grosse in particular, pointed out that if a condition is on the core set of screening conditions, that it would require a very high bar of evidence, of a lack of benefit for screening to remove that from the core panel. But others pointed out that that could be done if the data are there. It certainly could be done.

And so, there was a question of whether we should have some sort of, and this is not a new idea, but whether there needs to be some sort of active process to consider removing conditions from the core panel, and even more importantly to reflect what is the purpose of the secondary panel, and not have confusion about the secondary panel being intended to be targets for newborn's screening programs. And I think that's all of our

slides.

Is there another slide? Yeah. Thank you.

DR. CALONGE: Excellent, thanks Shawn, and thanks Scott. And let's turn again to Jannine and Siobhan.

DR. DOLAN: Thank you. While the slides are coming up I will just start based on the -- I'll just start while the slides are coming up. So on the evidence review process, families feel that the risk of uncertainty and the potential harm is overly valued by the Committee. And there's a sense of like annoyance and frustration.

Like why shouldn't -- why can't the Committee just bring up, there may be a potential harm, or this is uncertain, and therefore we're just going to shut it down. And the sentiment was like why is that you could just raise that issue and shut the whole thing down, versus why shouldn't that uncertainty and that potential harm be subject to the same evidence review as the benefits?

So they feel like it's a real double standard. And ultimately then feel that the information that's available, even if it's uncertain, even if we're not clear, parents have a right to that, because ultimately they have to make the decisions, and then they have to live with the

outcomes.

So there was a strong sense of feeling that it was just very maternalistic, but why should the Committee get to make that decision. The parents can process uncertainty. They can deal with uncertainty, and in fact they need to live with that, so they'd like to know it.

And that theme came up again and again. In addition, parents literally want an additional seat at the table, so there was a conversation about the fact that there's one parent representative on the Committee, could there be two? Final consideration, similar to the one I just mentioned about weighing, the issue of costs and who gets to weigh the costs.

Is it the public health cost versus the parental cost, something that anybody but the parent should be able to weigh in on. So again, parents strongly wanted to be able to make these decisions themselves, and not have others saying, you know, well that's just not ready, so you can't have that option to know this information. And then you need to live with the outcome.

Another sentiment that came up many times was the benefit of saving a life by getting a true positive sooner is so much greater, and cannot even

be compared to the risk of a false positive. So the sense from parents was that the Committee sort of, you know, weighs this as, you know, rather similar, and we need to look at them.

And the parents are saying they're not even on the same scale. And in fact, during this period of conversation a parent typed into our chat that she had had a scenario where her son had a positive screening test result, and she went through a whole period of grieving and mourning, and stress and anxiety regarding that, and then it turned out it was a false positive, and she then was able to, you know, reverse course.

And yet she agreed that even though that was a difficult experience, it can't at all compare, nor should it, to the experience of a parent who loses a child when screening would have saved their life. So that sentiment was loud and clear, and really reiterated by many of the family members.

And then the last notion was that families suggest that we just start screening. Screen for all these conditions, then we'll generate the data, and then people can look at the data and think about evaluation. But the idea that you could evaluate before you're screening is just not

realistic, and the family perspective is that screening is not such a big deal. Just start doing it and collect the data, and then we could sort of stop and contemplate and assess.

So that I thought was an interesting perspective that I wanted to voice on behalf of the families. Jannine, did you want to add at this time?

DR. CODY: Just to reiterate what Natasha brought up is the need for being able to quantify in some way through surveys or some metrics, the family experience that is being incorporated into the evidence-based review.

DR. DOLAN: Thank you.

DR. CALONGE: All right. Thanks for the summary Siobhan, and thanks to the family and advocates who participated in what sounds like a very rich discussion. I appreciate it. Let's go ahead and move on, and hear again from Michele and Susan.

DR. CAGGANA: Great, thanks, and while the slides are coming up I have a note here to reiterate as well what we just heard from Siobhan and Natasha, that we had actually talked about some way to incorporate the current perspective into the evidence review, at least to the package that gets

presented to the Committee in a thoughtful way, even though it doesn't file the rigorous evidence review requirements.

So, the slides are pulled, I will talk. So I'll get started. We talked about the fact that anecdotal stories are really absent from literature, and we get a lot of information, and Jacob talked about this as well. We get information from individuals when we talk to them on the sidebar. We hear anecdotal stories from clinicians during the discussions, patients, and even sometimes newborn screening programs.

And this information isn't usually captured in any sort of a publication or gray literature. And it's a big lift for a family to write a scientific paper. Typically, we'll see the discovery of the disease, we'll see the text for the version of the disease, and maybe later on, on a molecular basis of the condition. But after that things become sort of difficult to publish.

We used to be able to get case reports and literature, and you can’t really do that anymore. And so there's actual little to no information on actual counts and outcomes from at the outset or even it takes a long time even after your screening. And there's little to no data really on

the impact to society, or the medical system as whole.

We usually hear that as part of the testimony during the deliberations. So next slide. We also need to be cognizant that if we ask questions about newborn screening to the general public, that this discussion may actually reveal perceived harms that are really unrelated to the condition specific harms for which you're trying to get information.

And so that was just a word of warning that we sort of talked about that. You may get more than you asked for in some of these discussions. And obviously a lot of people talked about the issues related to the false positive results, and the late onset conditions generating patients in waiting, and that's usually one of the overarching harms that gets discussed.

We think one of the ways that we could work on this is to try and engage broad specialties, and a nationwide base of critical providers, sort of akin to what we talked about previously related to families, so that we could hear their perspective of harms and their experiences, and information on what their patients have actually experienced.

We heard when it was when we were in person from Dr. Tarini, how she and Dr. Goldberg talking about and studying issues related to harms from newborn screening, and we really felt that we would love to hear the results from those studies at the conclusion of those projects.

And with the expanding landscape of newborn screening now we are in a phase where we are identifying these late onset conditions in the family, just reiterating. So, if you have a late onset condition and you require long-term follow-up to determine if we could improve the test, and so you get into this loop that you really can't generate data prior to initiating the study, and so you really have to screen for quite a bit of time before you can get that information and improve the testing. Next slide.

We thought when we were trying to balance benefits and harms that you really have to equally consider both, and Jannine just brought this up. It's not a strict one and one in the harm and benefit may not outweigh, or equal sorry, any harm may not be full of benefits.

Should we give more weight to a false positive outcome than a diagnosis? And we talked about some examples of this, and one was

hypothyroidism, very common. One in a couple thousand in newborn screening setting. It also has a very high false positive rate. And so on some level, a high amount of false positive results seems acceptable.

But when you get into the discussion about rare conditions, if you have an equally high false positive rate for that, it's really deemed not accessible, not acceptable, and we really do need to have better tests and incorporate the second-tier test in sort of the style of what we've been doing over the past several years.

But we can credit the work of the Committee, that programs are really striving to develop highly specific tests, because the Committee has made some strides in actually defining what we screen. And we hear often from clinicians, and we often have to remind them that screening is not diagnostic. That there is a sense out there that screening is becoming diagnostic, and so the expectation is that the screening assay should be equivalent to a diagnostic assay. And if that doesn't happen, that's definitely a harm. Next slide.

So we also heard sort of the old natural history, which may not even be apparent for

conditions that are very rare. And then we have new natural history when it's related to early diagnosis or newborn screening, and this has been exemplified in the many sibling stories that we've heard from parents over time.

We had a hard time trying to figure out how we could measure emotional burden and suffering. We had a hard enough time figuring out the actual dollar cost when we try and get a cost for a screening test, the follow-up, the clinical evaluation, the diagnosis and then the following treatment. And so, we actually felt we really need the Committee to define, or someone to define for us really what burden incorporates. Next slide.

So we said definitions a couple times, we really do need precise definitions. And the question should be answered what programs should detect when they go through evidence review and any discussion, and we sort of have the gold standard of SMA where the test that was approved was nicely defined as an exome deletion.

We saw some of the confusion with SCID, and we still do where some programs only report true immunodeficiency, and other programs report a whole spectrum of immunodeficiency, based on where they established their cut-off. And we'll put a

shameless plug in here for counting conditions because again this will help us define what we're actually screening for, will allow us to develop more specific tests, and have reduced harm from this perceived false positive -- the harm from false positives.

We also talked about redefining RUSP conditions. If we look for everything we can find, if we do PKU screening and we get benign hyperphenylalaninemia (Hyper-PHE), and hyper-PHE and PKU and everything else in between we diminish our resources, and then that also affects the downstream ability to implement screening for conditions, especially as things are lining up at the door for to come into the evidence review.

So we really need to define what we're looking for. And also, the rush to screen. The pressure to implement screening as soon as things are added to the RUSP, and in reality, and this was mentioned as well, we also need to screen for several years in order to gather additional evidence, and then we need to do a final lookback. And so, this is sort of a do we have an improvement that will help us alleviate harms. Next slide.

When we talk about costs, costs change over time. We do need a formal process to review

them, and we have to improve the cost of the entire system. But we can only really in reality assess the costs of the time to review.

Things may change as things become more available and new treatments are developed and that sort of thing. And we felt that overall cost could be reduced if we establish a specific screening target, and so the onus is on us on the Committee to really define what we're looking for, and also the fact that costs are very dependent on geography.

We have rural versus urban, and sort of a nationwide difference of how costs are defined, and also the availability of services. We heard from a parent yesterday that they traveled, and they need to go to other states to try and get help for their children, and so that has to be appropriated as well.

And so, in summary we also have to realize that no matter how we change the process it's never going to be perfect. And I'm actually going to thank Kim and Leticia Manning from HRSA for helping us put this together, and Susan and our great group on the lab group yesterday, thank you.

DR. CALONGE: Yeah, what a great and complete consideration, and I appreciate your work,

and now we go to Jennifer and Colonel Hogue.

DR. KWON: Thanks. You can go to the next slide. So in terms of considering the different perspectives, I think it gets back to the question who are we doing newborn screening for? Traditionally, we have considered primarily the infant perspective, the child's perspective, but I do feel like we're hearing more and more about the family's burdens, and the need to reduce the diagnostic odyssey, how early knowledge can help in family planning.

The example was raised about Duchenne Muscular Dystrophy, how knowing that your first child has it can help you understand your risks with future children, rather than have the all-too-common situation we see in neuromuscular clinics where one boy is diagnosed, and then his younger brothers are diagnosed as well.

Using the same example of Duchenne, early diagnosis can help with early interventions, which can be valuable in terms of improving outcomes. So should the Committee consider broadening the scope of the benefits of newborn screening?

And, we certainly acknowledge what other groups have said that families want to know these diagnosis, and they want to have this access to

treatment. Next slide. I was trying to advance myself. So, how do we consider the harms of screening, given these different perspectives, and how do we balance the benefits and harms?

We recognize that false positives and screening creates some harms. One of the unintended consequences of these conditions being added to the RUSP are the patients in waiting that have been created, whose ambiguous health status creates a different kind of medical odyssey. The question of whether a standing citizens advisory group could provide additional perspective to potential harms of proposed newborn screening.

I did like the idea of a standing clinician's group as well. I think part of the difficulty with clinicians sharing their stories of harms is that we have a lot of concerns about privacy and HIPAA violations, and also sharing information about what may feel like frankly, malpractice.

And I think those are some of the things that never get talked about when we talk about harms of newborn screening. And should the Committee consider -- somebody brought up that the Committee should also consider the harms of those affected when conditions are not approved for the

RUSP, and again that gets to the family's pain of their condition not being identified as one that will be screened in newborns, and therefore more children will be born with those conditions.

Next slide please. So how can the Committee consider the overall burden of potential illness that might be averted? Is the evidence review, you know, there's a decision analysis that comes as part of the evidence review. Is that sufficient? Should we consider greater burdens?

We have estimates of the costs of living with disease that we heard about. We do less well in estimating the costs of early death, and the costs of a life, the quality of life should also be a consideration. And somebody brought up the use of disability adjusted life year analysis, and whether that should be incorporated in the evidence review.

Next slide. So how can uncertainty regarding screening outcomes be systematically considered given the lack of data, especially about potential harms, and then how should the costs, economic and opportunity be measured. I think I want to stress that in the evidence review they don't really look at cost.

When you look at, you know, the ability of

the public health system to implement screening, we look at the lives that are potentially saved by screening, and the decision analysis. We haven't really taken it on to look at costs. And in order to really do that in a fair way, and also to look at the harms systematically, we do need a robust long-term follow-up system.

So I felt that our clinician's group had two big funding asks. One was to ask for funding for more HRSA staff support at the beginning of the process, during the nomination phase, and the other was to really, you know, solve this problem of the lack of long-term follow-up data, for those identified by newborn screening.

One optimistic member thought that informatics could help for those of us who have, you know, seen how challenging it is to get this information. I'm not sure that there is a great solution. But could the nominators, or HRSA, at the time of the application provide some idea of longitudinal follow-up for the conditions in question. And could the pilot studies that are implemented for these conditions, or the states that are -- that have sort of implemented these conditions in advance of approval to the RUSP, could they share their ideas about long-term

follow-up. And could this discussion be part of the application package? That was part of what came up in that discussion.

Next slide. So what I thought I heard while listening was that the Committee should be aware of conditions where there's a treatment and a test that can be administered in newborns. And one of the criteria for the determining of the conditions belong on the RUSP versus under alternative ways of following children with heritable disorders apart from newborn screening.

So we discussed this in the nomination phase, and that the Committee should be proactive about conditions, and about long-term follow-up to help understand the impact of newborn screening. Thank you. I don't know if Jacob wanted to add anything to the discussion. Thanks.

DR. HOGUE: No, that's good. Thank you.

DR. CALONGE: Great. We're getting there. Some really good themes across the groups. I appreciate the comments were about children and newborns, and something to continue to keep in mind. CPSTF talks about additional benefits of intervention for community prevention, and so these side benefits are something that are part of the process, and figuring out how to include those, and

perhaps weigh them in the decision-making process could be important.

Committee Discussion

DR. CALONGE: I think considerations of what are the harms of not having a condition. I remember hearing that I'll say years ago, and so I think it's a good thing to kind of keep in mind as another item to weigh. I did want to make one point without valuing false positives over true positives, but the issue about rare diseases and false positives is a math issue.

So, if it's rare enough, a small percentage of false positives, a small false positive rate, will generate lots and lots of false positives, often to the point where there are more false positives than true positives. And so, that's one of the reasons why rare disease true positive, false positives are treated differently, just because of the way that the math works out.

It's not the rate, it can be the total number, so not to say that that should sway discussions one way or the other, but that's why they're looked at differently. So, those are just my initial comments. I could make more, but I'd really like to hear if there are additional

discussion items from the rest of the Committee.

Let's see. I'm going to start with Ash.

DR. LAL: My point that I wanted to bring up is many of the conditions are accepted based on the availability of a treatment, and many of the new treatments I think are going into the area of treatments are in the form of proprietary gene therapy interventions, as opposed to a transplant, or metabolic interventions, or other supportive care in the past.

The question of whether a treatment is FDA approved is different from whether or not families can actually access the new and approved treatment. And I think it will be beneficial for the Committee to know how the landscape of families being offered and then being able to access the new therapies is evolving over the next couple of years as more treatments come onboard.

DR. CALONGE: Thanks Ash, excellent point. I appreciate that. Bob?

DR. OSTRANDER: And I want to touch briefly on Scott Shone's comment that challenges in the healthcare system shouldn't be a barrier to putting something in the RUSP. I agree with him that sometimes coming out of the RUSP, you know, provides improvements.

However, but at the same token, I think in order to consider adding something to the RUSP, the Nominating Committee needs to look at is there a treatment available. That's pretty standard screening science, right? And so the question is are we talking about immediate treatment? Are we talking about immediate treatment and short-term follow-up? Are we talking about available immediate treatment short-term follow-up and longitudinal care? Which, at what level should we cut that off in considering the availability of treatment, and making a nominating decision?

I until today, after some of our discussions, have been very much in the advocate, saying it should at least be a blueprint or aspirational notion of what longitudinal follow-up looks like as part of a nomination consideration.

As I consider our discussion about that where the heritable, the Committee on Heritable Disorders in Newborns and Children, it occurs to me that maybe the RUSP decision is about immediate treatment available, or maybe immediate short-term follow-up treatment available, and then it becomes part of our obligation, separate from whether or not something gets added to the RUSP. It becomes part of our obligation to assess the longitudinal

follow-up of conditions that we've recommended be added to the RUSP, as opposed to making the longer-term longitudinal follow-up part of our initial consideration of evidence review, if that makes any sense, that someone points at.

DR. CALONGE: Thanks Bob, it made sense. Jennifer?

DR. KWON: Hi. Jennifer Kwon, Committee member. There were so many interesting ideas that came up. I wanted to address some of the comments that Siobhan made from the family listening session because I think this is another call for the Advisory Committee and HRSA to maybe think about how we present newborn screening.

So one of the comments I heard was that screening is easy. It's not a big deal. Why don't we screen to know, to give families this information, and they can deal with the aftermath. They're smart. They understand where to go and what to do. And I think that that is a mission that many people think that newborn screening should serve, that we should be a vehicle for early diagnosis for conditions that have potential treatments.

And I think that newborn screening is a public health endeavor, and as such, we have to

weigh the conditions that we're looking for. And we, you know, just sort of as Bob said, we -- should we focus on the short-term treatments? Is there something, you know, what should we sort of wrap our -- maybe I'm paraphrasing incorrectly Bob, but what should we wrap our heads around when we think about a disorder that we should screen for?

Should we share information with people knowing that not every family will be able to process ambiguous information, or difficult genetic data? Because it's their right to have this information, or should we consider it as more of an emergency program. An emergency public health program for conditions where very good treatments are available, and where children can really have a markedly improved outcome if they have access to them?

And part of the way to give them access is by early diagnosis. So I think that it sort of gets back to who are we? And what are we trying to do for families? I want to be equitable, and I want to share the process with others, but I also think that there's a public health mission, and part of what I think angers families is they feel that we're not serving them. We're not serving

that public health mission for them. Thank you.

DR. CALONGE: Thanks, Jennifer . Debra?

DR. FREEDENBERG: So, Debra Freedenberg, AAP. So I want to make a couple of specific comments, and some technical comments. But one of the things that's concerning in this discussion is that there seem to be some thought to shifting the responsibility to clinicians, both general pediatric care, who will have to deal with a lot of this, as well as with the specialist.

And I think we need to think generally that's the unfunded part of this system. And I think that we need to think very in depth about where the responsibilities will lie if some of these changes are made. And I had two sort of specific. One is I would caution people to consider the quality of life as a part of the decision making.

Most families that I'm aware of value the life of the severely disabled child versus the child that's no longer alive. So I think that we would really need to have a lot of caution in thinking of that.

And then the other thing is that for information about the various conditions that are being considered, almost all of these conditions

either have a parent group or a professional group that's available, and that information is out there. It hasn't been reached out to, but there are lots of you know, every sort of disease has its own either parent or some of the better organized groups.

But there is that information out there. And there have been attempts to do long-term follow-up and you know, in a data collection way, and those really have not been that well supported, and not that successful right now. And then my final comment is just about removal of conditions.

If we were to consider that in an organized way, I think we need to think about whether that condition is a technical issue, or is actually the condition itself. And for instance, you know, one of the things I'm thinking about is you know is tyrosinemia, the screening analyte was not very good, but then as technology improved, there was another analyte that was much more specific. It had a much better performance. So you know, it wasn't the condition itself, it was the technical aspects of the screening. And I think we would need to think about that as well. And finally, I think that this is an incredibly valuable discussion, and thank everyone for their

input because there is a broad spectrum of views.

And I think that as we consider this, you know, we've heard about long-term follow-up and natural history. I think there needs to be some sort of organized funding mechanisms to continue those studies, which apparently are not there anymore. So I will stop there.

DR. CALONGE: Thanks Debra, Jannine?

DR. CODY: Yeah. I'd like to add one thought to what Debra had to say about the sort of the burden to the clinicians for follow-up. When we talk about the diagnostic odyssey, we are usually referring to sort of the pain the families go through searching. But there's a huge cost to the medical system from going from doctor to doctor, and MRI and all these other assessments that get nowhere, or don't lead to a diagnosis.

So the diagnostic odyssey does have a huge cost to the system. So even though identifying additional patients has a cost, it also is offset by less diagnostic odyssey. Maybe somebody has some data on that. I don't know.

DR. CALONGE: I do think we should look at the EveryLife study that they provided as part of the materials. I think the other thing I always think about around diagnostic odyssey is that we do

have next gen screening.

We are newborns and children, and couldn't we consider putting together a diagnostic odyssey screening test that would capture most of the things that we worry about, so that we could do it at one point. It would be available to all clinicians, and would answer those questions in a more timely fashion, but not require screening the entire 4 million dollar newborn -- 4 million newborn cohorts.

So I think there are some other strategies that I would be excited to pursue as well. Sue Berry?

DR. BERRY: Thank you. Sue Berry for SIMD. I think one of our problems is that we are seeing ourselves as only having one tool, a big hammer, and one way to hit it to pound the nail. And I think Ned, you've kind of brought up what is I think something we should be thinking very hard about, which is a paradigm shift, that allows -- and the big nail, the big nail we're trying to hammer, carries with it a public health mandate.

Essentially, irrefusable those I understand it is refusable. Invocation of a test that's done essentially without consent. A lot of

the information by my own state, for example, I can't do genetic testing without an informed consent. It's written in our law, our state law.

The exception is that newborn screening elements that have DNA testing, but essentially if we were to add genomic screening, I'm not sure it would be legal in our state. I feel like what did I do here? Sorry. I feel like what we may need to do is really think much harder about a paradigm shift that will allow us to have our cake and eat it too. I'm using all these metaphors, terrible metaphors to say that we have to think about this in a different way.

We want to keep our effective and wonderful newborn screening strategies that allow us to really implement care on a nearly immediate basis. We've struggled to maintain that. We need a strategy where we can do additional ascertainment that's highly meaningful in a different time frame, and like with consent and likely not on everybody.

And so, I just think we need to think more broadly about how we consider the care of newborns and children, and as we do that we need to pay a lot more attention to the system overall. The system that's not just the screening and testing, but also the follow-up, the care, the access to

treatment, the people power that's required to maintain and support families on a longer-term basis.

And finally, a meaningful strategy for long-term follow-up. Tooted that horn so long you're tired of it, but we've failed miserably in that area. So, you know, thank you. Thank you for the opportunity to speak.

DR. CALONGE: Thank you, Sue. Shawn?

DR. MCCANDLESS: Yeah, thank you Sue. Excellent points, and Debra and other speakers. I just want to reflect on one specific point, and that is there's been -- there were a number of comments that came out of the listening groups today that I think reflected a desire on the part of some people to change the focus of newborn screening from being specifically directed to improving and providing therapy for the lives of individual patients that are affected with these diseases.

And I would encourage us to be very, very careful about broadening the scope of what newborn screening is intended to accomplish because for the reasons that Sue pointed out, this is a compulsory population-based screening program. It involves every baby born in the United States. And if we

start to say that as a Committee, or as a group, we're shifting the focus away from taking care of the babies, and making their lives better to other societal goals, whether it's for the family or for the society at large. I think we're opening ourselves to a lot of potential harm to the system, maybe even losing our mandate and support for compulsory screening entirely.

And especially in the current clinical environment. I think we just need to be very, very careful about how we, you know, what we do. And finally, I would ask the question of whether this Committee, we're certainly a reasonable place to have that conversation, to start that conversation, but we are not empowered, nor positioned to make the decision that the purpose of newborn screening is changing from improving the lives and delivering the lifesaving therapies to individual infants affected with a specific rare disease.

DR. MCCANDLESS: Thanks, Shawn. Jennifer?

DR. KWON: Just a quick follow-on to what Shawn said. I totally agree with Shawn's comments, and appreciate what Sue Berry said. I think that I really think we have to acknowledge the pressure that we're feeling about broadening the scope of what gets placed on the RUSP.

And I think that that's the best way to help us guide people through the nomination process, and help advocacy groups understand the purpose of the evidence review. But I think that there is a lot of pressure out there for us to broaden our scope and I think we need to acknowledge that as well.

We want to, you know, we want to respond to families who are in pain, but we also have to sort of think as people have brought up about this mandate that we have, and about this unconsented testing that we do, so that's all I wanted to say. Thanks.

DR. CALONGE: Thanks Jennifer. Paula?

DR. CAPOSINO: Hi. So I don't know what meeting I was in where somebody said that 20 percent of people have a rare disease. And it's sort of number one, I don't know if that's true. Number two, I don't know how much of that might be, you know, in small children.

I do wonder if this is a program that is going to be able to serve every need, and sort of the idea that maybe something, some of this belongs somewhere else because this, of a tremendous public health importance. And then the other thing is when there were discussions about removing things

from the RUSP.

I was just wondering if the idea was for the existing conditions, or sort of to bring in things where there's more uncertainty with the idea that there's this path to remove within a certain amount of time? I wasn't sure I understood sort of what the proposal was there. Thank you.

DR. CALONGE: Yeah, thanks Paula. So let me just clarify that. The actual thing is that there may be conditions on the RUSP, but now that we have for some of the decades of experience that if we actually reviewed both immediate and long-term care, we would say we're uncertain that we're providing that benefit, so they no longer meet the criteria for being on the RUSP, and should come off.

Way back in 2010, I made the suggestion that we consider a provisional category where we could add conditions, get some data, and actually make a better-informed decision. And just interestingly, it was pretty much rejected by the whole Committee at a time with the issue that we would never have the discipline to take a condition off.

And when I heard the phrase, "the bar to removal would be higher," that reminded me of that

dialogue. So, it's not that we didn't talk about this concept of let's put it on and get some experience. It was a worry that we would not have the ability or the discipline to take something off once it was added.

Or is it something that could be re-discussed because these are within our purview. Shawn?

DR. MCCANDLESS: Yeah, just a very brief comment about that. I don't really think there's anything on the core conditions that anyone would significantly argue should come off. I think it's the secondary panel.

DR. CALONGE: Yes.

DR. MCCANDLESS: And, you know, I've made this argument in an earlier meeting that we should just get rid of the secondary panel, and that everyone was polite, and nobody pointed out to me, but should have, that it's actually in the law that embodied this Council, that there be a secondary panel. So we needed some other solution to fix the secondary panel problem. And the problem is not with the panel.

The problem is with the way it's understood by the community to be targets for newborn screening when in reality they are

specifically not the targets of newborn screening, they're the incidental findings that you'll come across when you're screening for things that are the targets of newborn screening. And it's just to create awareness, and unfortunately it's been broadly misunderstood by the medical community as well as by the population as a whole.

DR. CALONGE: Thanks, Shawn. So Michele?

DR. CAGGANA: I just -- this Michele Caggana. I just wanted to reiterate the discussion about the secondary conditions. I think the other thing we have to remember is some states have it actually in their law that they shall screen for these, and so just removing them would be quite difficult, and again it feeds back to just being more comprehensive in counting conditions, thanks.

DR. CALONGE: Thank you. I'm going to draw us to a close for this part of the meeting. It's been absolutely fantastic, and I think it's safe to say that as we look at the slides and the summaries, it's going to take us some time to work through the scope of the discussions.

There are a couple things I'd like to have us think about moving forward. We only have limited time for each one of the sessions. We gave you a group of questions that in some ways I was

worried were too many to address, but people managed to seem to get through them and provide a lot of feedback.

I'd like to suggest that we schedule additional listening sessions at future meetings, and also post a Federal Registry notice to get written feedback to delve into more detail, and to get a little bit more clarity and direction in moving forward.

Also, I think based on what Shawn is saying I'd really like the Committee at this time to think about this issue of let's get Krabbe and DMD through the process. But we should consider pausing on new nominations as we look at the process, and we consider all of the changes we believe we need to make, including to finding our role as a Committee beyond what's currently in the law, or at least specifying that and figuring out ways can we be more efficient, more inclusive, and meet our mission a little bit better than I think we are now.

So, those are just two things I'd like to throw open to the Committee and see what people's appetites are. Michele, is your hand back up, or? I did inquire, we have the ability as a Committee to say we're taking a pause on new nominations

while we review our methods, our approaches, and consider a lot of the elements that we've discussed over the last couple days. Jennifer?

DR. KWON: Thanks. Jennifer Kwon, Committee member. Can you remind us when we will be voting on Duchenne and Krabbe, and also how long a pause you were envisioning?

DR. CALONGE: Great. Both great questions. So, I think if we start, the nine months would have started at the last meeting. So when was that? May, so it would be nine months. Then we would vote on both conditions, and I was thinking something around a six month, certainly no more than a nine month pause, but about a six month pause to try to do the work and focus on not only getting DMD and the Krabbe expedited review finished up, but also taking on a lot of the work that we need to do in redesigning and reidentifying the way we do our work. Shawn?

DR. MCCANDLESS: Yeah. Maybe I just need a little more clarification. I think there's two components to the work that we're discussing. One is the changes that have been proposed to the decision matrix, and the process for moving things forward to recommendation to the Secretary of HHS. That's one thing.

The second is the discussion about updating or changing the nomination process. It feels like the work on the first part is more advanced than the work on the second part. So I guess I would say, and then I'm reflecting on the fact that I think we heard yesterday that there is either an application received, or on its way for biliary atresia, congenital biliary atresia, so that one we probably need to make a decision about how to move forward.

But I would propose it if there's already a nomination and it's been received, that should continue under the hold, at least the nomination process. And I think a six month pause of the -- a six or nine month pause on the decision-making process that excludes DMD and Krabbe, so that if they move forward through evidence review, we'll review them under the old decision matrix.

There shouldn't be anything that requires the new decision matrix for at least six to nine months gives us -- there's no feasible thing that could come before us that would require a vote before then, so I think it would be reasonable to say that anything that's after DMD and the Krabbe rapid review. Anything after that would be under the new decision matrix, and that we would set sort

of nine months, or a year as the hard stop for making that happen.

DR. CALONGE: Yeah. I think that was my intent, Shawn, you just summarized it a little bit better. I think, you know, we're very close on the decision matrix. Other than kind of taking in all the information we had on weighing benefits and harms, and what information feeds into both of those buckets.

So I think those are kind of outstanding elements on the decision process, and then the nomination process as you've talked about. And again, I will not -- I want to assure that the rules that DND and Krabbe entered in will be the rule set that sees them out the other side.

And I think you're right about the basic time it will take to take through the biliary atresia, so thanks. Michele?

DR. CAGGANA: The other thing that we need to be cognizant of as we heard yesterday, and we've heard a couple times about groups that are preparing packages, and understanding that these packages take an awful long time to develop. And so, they are working on developing them through the old procedure, and it would really be a whiplash, I think, for them to now pause. And so I wonder if

we could, you know, if you're in the door by May, kind of do that process.

I don't know how to situate that, but I think we just need to be cognizant that as it stands now the nomination process is very lengthy for people to submit, and they're down various paths to do that. And so it would be difficult to get them at a hard stop for a period of time. Just something to think about.

DR. CALONGE: I did think about this for a long time, especially after listening in yesterday. And the issues we have to draw the line at some point. And that's my worry is that no matter where we do it, there's going to be what I want to say, people that will feel disadvantaged versus privileged, so I guess my approach was that we have two that are entered the process under this current rule set, and that would be my approach.

But this is a Committee. I would like to get an idea of where the Committee is at as well. So, I know where you are Michele, thanks. Shawn, are you commenting on this or?

DR. MCCANDLESS: Yes. I'm wondering if maybe the middle ground here. So the decision matrix is clear. It seems very clear. That's not going to be a problem. It's really the nomination

package, the nomination process, and I don't have a good sense of what the timeline is going to be for this, so I think maybe the middle ground would be to also put a pause on new nominations that starts now, but have a mechanism in that process for groups that are in the process of preparing a nomination to reach out to HRSA, and work with the HRSA staff about which process they should be planning to follow.

Should they -- if they haven't started, we would recommend they wait for maybe as much as nine months to a year for the new nomination process to be put in place. And again, I'm specifically thinking about MLD, which Dean Suhr indicated yesterday that they are working on a -- you know, that they are anticipating a therapeutic that has benefit, documented benefit, and that they're working on a package already. That would be an example of a group, and I don't mean to call them out specifically, but that would be an example of a group that we should say talk to HRSA staff, and you all make a decision about what is going to be most appropriate for that condition.

Other -- there may be other nomination groups that are working on something that we're not aware of, that might want to also reach out to

HRSA, but it seems to me that that's going to be the simplest way to handle that, so we put a maybe even a one year moratorium on new applications with an option for people that are already working on a nomination package to reach out to HRSA staff for a case-by-case evaluation of where things stand, and how to proceed for that package.

DR. CALONGE: I think that's a great middle ground, and I think it's something that we -- no one is kicking me under the table, but I believe we could implement. Great, well again, it's been a great discussion. I can't -- I don't think I can do justice to how much I appreciate the work that everyone put into the sessions yesterday.

And then to our folks who were volunteered to actually sit in and summarize those, and then the presentations today, and the thoughtful discussions were just outstanding. Shawn?

DR. MCCANDLESS: I just realized that Scott and I did a terrible job of acknowledging Akila and Monica who worked with our listening group yesterday, and everyone else did such a good job. Would you be willing, Ned, to tell us all of the staff people who acted as facilitators, or note keepers, or have Leticia, just so we can all give them a big thank you because it sounds like

everyone was number one, went above and beyond the call of their job description to do this. And number two, did a terrific job.

DR. CALONGE: Yeah. Leticia, can you?

COMMANDER MANNING: I can. So thank you so much for giving me the opportunity to provide some kudos to my wonderful colleagues.

For the Public Health Group we had Akilah Heggs, I hope I'm pronouncing her name correctly, and Monica Adderly. For the Clinician Group we had Mandy David and Lisa Song. For the Laboratory Group we had Loraine Swanson and Kim Morrison, and for the Family and Family Representative Organization Group we had Donna Johnson and Ajee Johnson, so thank you all if you're on. Thank you so much for your assistance.

DR. CALONGE: And thanks Shawn, for helping me be a better Chair than I really am. So I think we've heard a five minute break, sorry. And the only reason I say that is we're a bit behind. When we come back we're going to have updates, phase one updates on DMD, and Krabbe, and then we will bring Jelili back to give us an update on the work that APHL is doing in the counting conditions and other activities.

So I have about a quarter to 12 hour, and

then we'll come back and try to resume right there promptly at 10 minutes of the hour. Thank you.

APHL Updates

DR. CALONGE: I'm sorry. We are back. I would like if he is with us, to start with Jelili.

MR. OJODU: Good afternoon, good morning.

DR. CALONGE: It's great to see you, great to see you.

MR. OJODU: Same here.

DR. CALONGE: Go ahead.

MR. OJODU: So, I have the good fortune of giving a quick update on some of the activities that we're embarking on as part of Newborn Screening Excel, which is also known as Newborn Screening Technical Assistance and Evaluation Programs NewSteps. We've had the good fortune of having some supplemental funds to be able to address a number of things that have been brought up as part of the discussions over the last several meetings of the Advisory Committee.

I'm going to try my best, I don't have any slides, just to quickly go through this. These activities have just been funded, and just give you a brief high-level overview of some of the things that we're working on. The four things that I want

to highlight are counting conditions, which you've heard quite a bit on, counting and naming conditions I should say.

The second thing is going to be on second-tier testing, or secondary testing. Higher testing for conditions in newborn screening. The third thing will be related to health equity and newborn screening, and finally I'll briefly mention family outcomes.

So, as part of the supplemental funding that we receive some HRSA, and thank you HRSA. We are able to continue on trying to address commonization and uniformity of how state newborn screening programs name and count conditions. And I don't have to say this to anyone, but you can go on different websites, and different people count conditions differently, whether they're adding the core conditions with the secondary panels with treatments and other conditions that they think are part of the newborn screening program.

At APHL and I think in 2021, we on the workgroup were to be able to look into this, and the activities that we're going to embark on over the next year, year and a half is going to look deeper into how we can better count and name conditions. I think if you look on the RUSP you'll

see that a number of conditions are just named, are classified as other, and if they don't fit into any one of the other categories or disorders, whether it's the endocrine disorders, or fatty acid oxidations, or lysosomal storage disorders.

The work related to this means that we bring people today, communities of practice of the newborn screening systems, and that's exactly what we're going to do. We formed a group of individuals, I think 19 in all, for different aspects of the newborn screening system to be able to address this.

They will have the opportunity to meet in person. This will also include people from the Advisory Committee, and we hope that we can report back to you all on some of the activities and how we are addressing this in the form of outcomes in future Advisory Committee meetings.

The second thing quickly, is related to second-tier testing. A number of conditions that we screen for as part of our Recommended Uniform Screening Panel, our state panels require some form of second-tier testing to be able to reduce false positives, among other things, and to be able to reduce that burden of calling out a positive when it isn't, to those families.

We've heard quite a bit about harm, to reduce that harm in that sense. We know that not every state has the capability or capacity to be to second-tier testing, or higher tier testing. We also do know that it's quite important in a number of conditions that we screen for.

And so, a number of us have been thinking about how we can better assist all the newborn screening programs anywhere around the country to be able to, you know, what is available, understand the costs, provide peer network review centers, or centers of excellence that can be able to provide quality second-tier testing, higher tier testing for any state.

This project is currently under what we call Newborn Screening New Disorders Work Group, and we've also just formed a committee and a charge to be able to address this. And again, this work will span over the next 12 months, and we will report back to you all on some of our activities and successes, and challenges as well.

There was a great presentation during the last Advisory Committee on health equity. I think it was Dr. Houtrow from the University of Pittsburgh who gave a wonderful overview focusing on equity in newborn screening. This is something

that I know HRSA has, we've heard quite a bit on the investment to be able to look at equity, how equity across newborn screening systems, especially for the conditions that we screen for, and other conditions that we're thinking about screening for.

Equity in just making sure that, you know, whatever is provided for any individual that is screened is the same regardless of circumstance. And so, we're thinking about a number of ways to be able to address this. One of them is starting, and you will see an email shortly from us, a community of practice related to health equity in newborn screening.

Similar to how we built a community of practice to follow-up where we now strongly advocate for follow-up, whether it's longer or short-term follow-up in moving forward, we want to be able to build a community of practice and want the individuals to be able to discuss the kinds of things that Dr. Houtrow mentioned, and come up with some ideas and solutions in a collaborative way, so more on that in the coming year.

And then finally, the last one of the activities that we're going to be embarking on as part of this supplemental fund is assessing and developing what should be measured as part of

newborn screening long-term follow-up and quality of life. We will be working primarily -- we'll be carrying most of the load here with RTI to be able to address this.

We don't have much, I don't have much to update you all on, on that, but I can assure you that we will be working with the newborn screening community. I think we are engaged with a number of regional networks in their current form right now to be able to address this particular activity moving forward.

So I just wanted to give you a brief update on some of the things that especially as it relates to what the laboratory, former laboratory subcommittee was working on, and something that has now been punted to us, and we take on that challenge gladly as an association to be able to work with a number of partners, to be able to address moving forward to any of those out there.

DR. CALONGE: Thanks, Jelili, for that great update. Are there any questions for Jelili? See, you answered all the questions, so thanks. That was great. Let's go ahead and move on.

Duchenne Muscular Dystrophy Evidence-Based Review:

Phase 1 Update

DR. CALONGE: I will just remind everyone that Dr. Alex Kemper is a lead on the Evidence Review Group. He's also Division Chief of Primary Care Pediatrics at Nationwide Children's Hospital and a Professor of Pediatrics at the Ohio State University in College of Medicine.

His research focuses on the delivery of preventive care services, including newborn screening. And since 2013 he has also served as the Deputy Editor of Pediatrics. He's going to start with a phase one update on the DMD evidence based review. Dr. Kemper?

DR. KEMPER: Dr. Calonge, thank you very much for the kind introduction, and I'm delighted to be here today. As you mentioned, I'm going to go through with what we call the phase one summaries of where we are first for Duchenne Muscular Dystrophy, and then for Krabbe disease. These particular presentations are designed to be very high level, and are going to tee us up for subsequent meetings where the Committee can dig into issues related to screening for the condition, condition outcomes, and so forth.

So again, these will be quick presentations. Next slide please. So first of

all, I want to thank the members of the evidence review group for the hard work that they're doing, and I also want to thank the Advisory Committee liaisons for this project, Dr. Dorley and Dr. Phornphutkul. Next slide please.

As we do for all of our project, we have a technical expert panel. This is a slide of those who have agreed to participate in our technical expert panel, and it really covers the waterfront from the experts in screening, experts in diagnosis, and experts in treatment for DMD. It's really quite a vibrant and really knowledgeable group. Next slide please.

So I just want to give a little bit of background. Again, the purpose of this presentation is to tee us up for the subsequent meetings. Next slide please. So, as I think everyone knows, Duchenne Muscular Dystrophy is an ex-linked progressive disease, characterized by loss of muscle function and weakness. And it's caused by variants in the *DMD* gene.

The *DMD* gene codes for dystrophin. Dystrophin appears in multiple tissues, but primarily is expressed in muscle, and again is the major focus for the review. One of the things it's important to recognize is that the truncated gene

can have some function, and you'll understand in a second why I bring that up.

Affected males, typically begin to have weakness in the first couple years of life, followed by progressive loss with loss of ambulation in early adolescence, and later support in early adulthood. And life expectancy can be highly variable. I've listed 18 to 41 years of age, and some of this depends on the kinds of interventions that they have received. Next slide please.

As I mentioned, *DMD* gene codes for dystrophin, which is the longest gene that we as humans have. It's two and a half million base pairs long. It leads to dystrophinopathies, DMD which affects between 16 and 20 per 100,000 males. It can also affect females, but it is much more rare. Females can be carriers who can also have functional problems, again we'll be talking more about that in subsequent presentations.

There's also Becker Muscular Dystrophy, which is a less severe phenotype, and it's also less common with incidents of about less than 8 per 1,000 males. Individuals can also develop x-linked cardiomyopathy. Next slide please.

So here's a screening. Next slide. It's

primarily based on identification or measurements of creatine kinase, which is also known as creatine phosphokinase. Creatine kinase has two subunits with a muscle type and a brain type, and the particular isoform to target in screening is CK-MM, that is two muscle subunits.

When CK-MM is elevated, then second-tier screening can help with establishing the diagnosis. So there's *DMD* sequencing, which we -- let me preface it by saying that since these slides were put together we had a wonderfully rich first technical expert panel call where we spent a lot of time talking about this issue of genotype phenotype correlation.

And you know it was the strong belief of the technical expert panel that if you have persistent elevation of CK-MM and particular mutations, then you can make a strong argument about the linkage between genotype and phenotype. And so a more evasive, confirmatory test like muscle biopsy is not needed.

Now again, we're still going through the evidence right now, the published evidence to look at issues of genotype phenotype correlation, but I did just want to add that in. But historically, muscle biopsy needed to be used a lot, and now it's

much less so the case.

The other thing that's sort of hot off the press since I had to submit this is that as you can see that I had “no state which currently includes DMD newborn screening.” New York did just pass legislation to begin DMD newborn screening, but it's not been implemented quite yet.

And then there have been a lot of other population screening programs in the past, and some smaller screening activities that are going on. Again, we'll talk about this in the next meeting when we drill into things further. Next slide please.

In terms of treatment, next slide. There is supportive care, which you know, could be given across the lifespan. These include physical therapy, maximizing nutritional management, speech and language services, involvements of other specialists, for example, pulmonologists, and cardiologists, and then orthopedic and other system devices as needed.

There's been a lot of work around pharmacotherapy, historically the mainstay intervention was the use of glucocorticoids to reduce muscle damage and stabilize muscle cell membranes, which could slow the progression of the

muscular dystrophy.

There's a new steroid that's recently been approved for the use of Duchenne Muscular Dystrophy, so although glucocorticoids historically have been the mainstay therapy, beyond the supportive care. There are some new therapeutic options available.

There are also exon skipping drugs. We are now drilling into a better understanding of the proportion of individuals with Duchenne Muscular Dystrophy who have benefitted from these exon skipping drugs, and looking at what's known about early intervention with these drugs.

And then there's gene therapy. Gene therapy involves a smaller version of the dystrophin gene. You can't actually pack the whole gene into the viral vector, and so gene therapy leads the production with what's referred to as a micro-dystrophin.

Again, we are busy looking at the evidence regarding the benefits of gene therapy. Gene therapy right now is only FDA approved for children who are four and five years of age. Next slide please.

So in terms of our ongoing activity, next slide, we are working through a literature review.

Unlike some of the other conditions that we've looked at there's a lot more published work out there, so there are about 7,000 articles that we're going through to see which ones shed light on the potential benefits of newborn screening.

We held our first tech call at the end of October. We've begun the process of our key informants' interviews. Our plan is to conduct the public health system impact assessment in early 2024. We're working with the development of the decision analytic model as we always do, and then you know, we're having challenges that we will work through both on the evidence, as well as with our liaisons, and the technical expert panel in terms of the right outcome measures, both for the review overall, as well as for the decision analytic model.

And also the appropriate time horizon for the decision analytic model, which will be based on how far out the evidence goes related to early intervention. Next slide please. So I will stop there, and just see if anybody has any questions about the progress we are making, and of course I'm always happy to set up separate calls if any Committee member has questions, and certainly answer emails. Dr. Kwon?

Committee Discussion

DR. KWON: Hello. Jennifer Kwon, Committee member. So, when do you think, when did you feel like your deadline was, because it seems like you might be going a little further out than the February meeting?

DR. KEMPER: Well, so there's not assigned to it, so the February meeting would be the second presentation, and then it would be the one after that that the vote would occur.

DR. KWON: Okay.

DR. KEMPER: That keeps us in the window.

DR. KWON: Right. Alrighty.

DR. CALONGE: Other questions? Thanks Alex, for this first look. It was an invigorating call, and the follow-up email chains have been interesting as well, so appreciate everyone's work, especially subject matter experts, and other folks that are contributing information.

DR. KEMPER: If I can do so, I just want to thank you again, publicly thank those who volunteered their time with the technical expert panel. Like we would never be able to do the work without them, and their great engagement is really critical.

DR. CALONGE: So, Alex, could you move on to Krabbe?

Krabbe Disease Expedited Evidence-Based Review: Phase 1 Update

DR. KEMPER: I could once the slides are up. There we go. So this again is going to be a very high-level summary of where things go. Next slide please. Again, I'd like to thank members of the Evidence Review Group, and especially like to thank the Committee liaisons, Dr. Kwon and Dr. McCandless. Next slide please.

We have reconvened our technical expert panel, this is the same technical expert panel that we had before. We have not had a call with the technical expert panel yet because we're waiting for some other information to come in and that will make sense in a second. Next slide please.

So, just to remind everyone about the previous recommendation. Next slide please. So in February, the Advisory Committee voted against recommending to the Secretary that Krabbe disease should be added to the RUSP. That follows a timed vote. And in the summary from the Chair, highlighting opportunities to address gaps.

There were three specific things that were

called out. Additional information about the efficacy of stem cell transplant for early infantile Krabbe disease, more information about the potential harms of transplant that was begun early as a result of the screening, and additional information on outcomes for infants who are at risk of late infantile Krabbe disease. Next slide please.

So based on a request for an expedited nomination in May, the expedited review was handed off to us, as I think everyone knows. It's the first such expedited review. Next slide. And the key thing in the new nomination, the revised nomination I guess I should say, was the focus on infantile Krabbe disease defined as onset in the first year of life. And based on finding in newborn screening of reduced GALC activity in the dried blood spot, as well as an elevated level of psychosine in that dried blood spot.

So, just to highlight this again, the current nomination is much more prescriptive around the target of screening in an effort to reduce cases that don't fall under this definition of infantile Krabbe disease. No longer included in the nomination for example, is looking at the 30 KB deletion that we talked about before, and again

it's very specific about the psychosine level of 10 or more in the dried blood spot.

There are several state newborn screening programs that have now adopted a similar approach for gathering data from these states to better define exactly how their process works. One thing that I'm going to be very careful about, especially as we come out to the vote is just making sure that we don't use ambiguous terminology because we can get confused when we talk about infantile versus early infantile, and late onset and so forth.

And so again, following along the nomination, I'm using the term that they use, which is infantile Krabbe disease, which is onset before 12 months of age. And again, the hope is that with this well-defined criteria for screening that these are the infants that would be identified through newborn screening. Next slide please.

So, now I'm going to sort of go over the process. Next slide please. So, for our expedited review, again we're going to focus on what's been nominated in terms of the screening tests. We're conducting a brief search of published data that is what came out since the last time we looked at things.

We are also looking for new unpublished

literature that meets our criteria that can weigh in on those things. And I have spoken to one expert in the field who is working on a study that's going to be a standardize assessment in development of subjects with Krabbe disease that were identified through newborn screening, and treated with transplant in early infancy.

That study is going on right now with a plan that it will be submitted and presented at a national meeting, and will be able to be included in our literature update by the time we convene again in February.

Again, as I mentioned before, we've reached out to the states that are using psychosine as a second-tier test to learn what their experience has been in terms of the cases that have been identified and their positive predictive value with that strategy, as well as really trying to drill into those cases that have been identified through newborn screening that meet that screening bar that we've talked about before.

So, the nomination letter identifies 11 cases that were identified. We again, are collecting data to find out how many cases have been identified, if there are additional cases out there we really wanted to learn anything that we

can about them. And then the next thing is that we're updating our decision analytic model to reflect the new target of screening, a much more specific target as I've mentioned a few times.

Next slide please. So I'd like to leave things open for questions. Oh, Dr. McCandless? Oh you're on mute, which will allow me to replace it with an easier question I think.

Committee Discussion

DR. CALONGE: Oh. Something's happened to your microphone. Now you're on mute now. Now try.

DR. KEMPER: Or if you would email it to me really fast I can do a dramatic reading.

COMMANDER MANNING: We're trying to get you a phone number.

DR. KEMPER: Well, I guess while we're working through this technical difficulty, does anybody else have any questions?

DR. CALONGE: Sue Berry?

DR. BERRY: Sorry, wrong button. Minor points just to mention it, the great state of Minnesota has elected to add both Krabbe and Duchenne to their screening panel, so you may wish to reach out to them. They have begun the implementation process for Krabbe.

DR. KEMPER: Great. I heard it was under debate, but I didn't realize that the DMD had been added.

DR. BERRY: Yeah. So you might want to add them to your list of people to query.

DR. KEMPER: I will definitely do that.

DR. MCCANDLESS: Are you able to hear me now?

DR. CALONGE: Yes.

DR. KEMPER: Oh yes we can.

DR. MCCANDLESS: Sorry about that. My question is it seems to me that the new, the updated recommendation about the target of screening is changing. It's ostensibly infantile Krabbe disease, but it's specifically defining that by the newborn screening criteria of a psychosine greater than 10.

And my question really is maybe for -- maybe it's for the HRSA staff, or someone other than you, Alex, but is there a mechanism for this Committee to say to require that a newborn screening lab in a state who gets a value for psychosine that's 9 in a patient with low enzyme activity?

Can this Committee prescribe them from calling that out? Because the whole point of that

is to reduce false positives, and reduce patients that are not clearly, that don't clearly have infantile form, but that we don't know what they have, and therefore they get highly medicalized first years of life that may or may not bring any benefit to the individual subject.

And so the question is, is this an artificial distinction that looks good on paper, but doesn't actually solve the problem in real life?

DR. KEMPER: I think that's a question for you, Ned.

DR. CALONGE: Great question. Well, I think I'm going to have Jeff talk about “the authority,” and then I'll weigh in, thanks.

DR. BROSCO: And I'm just going to defer to Dr. Warren if he's available, if not I will jump in. All right. So we provide -- remember, this Committee does provide recommendations to the Secretary for adding conditions to the RUSP, and states then decide themselves what it is exactly that it wants to screen for and how. And it might even be worth hearing from one or two of our state lab partners about how they make decisions about these things.

And of course, if some states report of a

sickle cell trait, which is not on the RUSP. So what states decide to report or not is really in their purview. We provide guidance, and so our evidence review should be based on the nomination package.

DR. CALONGE: And I appreciate that. So let me say it a different way. We don't have the authority to do that, so at least start, that's a very concise answer to your question. We have been, I think, debating whether or not this shows up as a potential harm. And since we're being prospective about what we say is a positive test, it's hard to figure out where or how to weigh it as a potential harm.

And so, I think the technical expert committee, and the ERG group will wrestle with whether or not there's a way or a need to capture that as a potential harm, because we're saying don't do it. So, and your question is states will do what they will do, which is true.

So do we need to think about that? I guess you know, from my standpoint I wouldn't want it to be a harm that got elevated to the point where we weren't looking at the evidence for the specific test that we're recommending. So that's the way I look at it, but I think it is an issue

that we're aware of, we're concerned about, and we can collect some information, and ultimately will have to make a judgement whether or not it impacts the decision or not. Ash?

DR. LAL: So, just to pursue this issue of borderline testing, Dr. Kemper, in your review do you think psychosine levels are bi-modal, or is it just an arbitrary distinction here, are there any different --

DR. KEMPER: Yeah. What I can say is the last time we looked at Krabbe disease for you know, the previous nomination. We looked at all levels of psychosine, and there have been expert groups that have weighed in to develop algorithms for the management, and they set this psychosine level of 10 or more as being strongly predictive of having the infantile, or the early infantile form, and that there is a lower level, so between 2 and 10 where infants are at risk for perhaps the less severe phenotype, and would require more follow-up.

But that's where the level of 10 came from. Now, from the previous report, the infants that had the more severe phenotype, really had very much higher levels of psychosine. It wasn't like things were close to 10. They were pretty high, and so I think it's sort of the way to the expert

opinion that setting things at 10 is really going to capture those, all the infants are going to go and have a severe phenotype. Does that answer your question?

DR. LAL: Yes, it does. And it's just that part about how to report out the results that are below the threshold that are still quantified. But that's true for a lot of other conditions, I'm going to guess it's not just Krabbe.

DR. CALONGE: Correct. One of our, yeah thank you. All right, Alex, again great work. Great work and input from the experts, and we're looking forward to the next presentation as we move forward. At this point I would like to see if any Committee members would like to bring up any new business? Scott?

New Business

DR. SHONE: Thanks Ned. So, I wanted to bring to the attention of the committee, the ongoing lawsuits that newborn screening programs are facing, particularly around the use of dry blood spots. I think everyone is aware of the ongoing Michigan lawsuit that is now going to federal appeals court, and then yesterday there was a lot of news around a new lawsuit in the state of

New Jersey.

You know, I'm the org rep for ASTHO, not APHL, but I am a member of the APHL Board of Directors, and I am aware that APHL is working on an amicus brief in support of the State of Michigan.

I think it is imperative that the other organizations that have a strong and vested interest in the success of the newborn screening programs and the importance of these dry blood spots, and how they are used for program improvement and to save lives, as we've been discussing the last few days. You might want to reach out to APHL to see how they can continue to support them, or endeavor in their own opportunities in conjunction with the Michigan State Department of Health and their newborn screening program. I think this is critical, and I would ask all the org reps to go back to their organizations and see what they are doing, as I've done, to make sure that we are front and center on this.

This issue is serious, and it does jeopardize the successes that we have spent so much time, not only the last two days, but in our careers trying to make sure that we protect. So, I

would encourage everybody to do outreach, whether it's to Jelili at APHL, or Michigan Department of Health, to see what you can do to assist in this important program. Thanks.

DR. CALONGE: Thanks, Scott, and that's a very important announcement, and I hope folks think about it and reach out to APHL. Shawn?

DR. MCCANDLESS: I'm going to change the topic, so if there's other discussion about that issue, I'm happy to wait.

DR. CALONGE: Change away.

DR. MCCANDLESS: Okay. Yeah, I want to bring to the attention of this Committee something that's happening at the FDA, regarding some rules that they have had in place for laboratory developed tests that are -- and there are a number of people nodding their head, a number of people on this call that know about this already.

But in the past, tests that were most of the tests that we used for diagnosis and confirmation for rare diseases, including newborn screening conditions, are not available as commercially validated kits, and so the FDA has had -- has allowed discretion in how they regulate those laboratory developed tests in the past.

And there's over the past several years

been several efforts to tighten up their enforcement of oversight and monitoring of these laboratory developed tests. To the point where there's great concern in the field of people who do these tests for rare metabolites, enzyme assays, rare genetic tests that the requirements, the regulatory requirements that the FDA is proposing to be added may make it impossible to continue doing these tests because of the need for FDA validated and approved methods for doing the test that would be beyond the scope of most of the labs that are able to do the test.

There's a very real fear in the community, and it's not just a fear, there's a very real unintended consequence of this action that could result in the confirmatory tests, for example, psychosine measurement for Krabbe disease disappearing because there are not FDA approved kits, or FDA validated methods for doing that.

So, this Committee I don't think is able to move on that, but I just want to bring it to the attention of everyone on this Committee that this poses a very real threat for newborn screening. It's entirely possible that much of our diagnostic capacity will go away if the FDA moves forward on this plan to enhance enforcement of the regulatory

environment around the laboratory developed testing.

So, and again, I'm not the world's expert on the issue, but I would ask everyone locally to speak with your laboratory directors and others to find out what, you know, how this impacts your particular follow-up program, and consider whether there might be some action that you would take.

The FDA is accepting public comment, I think through December 4th, so we need to move fairly quickly on this as individuals or groups. Thank you.

DR. CALONGE: Thanks, Shawn, and I think hopefully we could get some more information too about this, and where it's at in the public comment period and the potential impact on newborn screening. Thanks for bringing it to our attention. Cindy?

DR. POWELL: Yes. Cindy Powell, ACMG organizational representative. I just wanted to support Shawn's statement. While the ACMG is very, you know, concerned about the accuracy of genetic and metabolic testing in children, you know, we are concerned about the proposed FDA regulations of laboratory developed tests, and what this might do, not only for newborn screening, but also access to

testing for children with suspected rare diseases.

And so, I do encourage everybody to give their input as Shawn said, the FDA is only allowing public comment until December 4th, despite our organization and others requesting a longer period of time to look into this. And I would encourage the FDA to look at the evidence for the need for this new type of regulations.

What I've seen so far, I think it's some of the evidence is more what's been in newspapers, and public discussion areas, and not so much in true evidence, so thank you.

DR. CALONGE: Thanks Cindy. Jelili?

MR. OJODU: I just wanted to amplify everything that has been said by Cindy, as well as Shawn, and Scott. The issue about residual dry blood spots is something that we all need to be not only aware of, but need to act on appropriately.

As it relates to the enhanced proposed regulations by FDA, I don't think I need to spend too much time reminding this Committee that if it wasn't for LDTs we would not be screening for -- it would take us a long time to be able to – not the confirmatory tests, the initial primary tests for SCID. And it took at least a little while for our corporate partners to be able to develop an FDA

approved test, so APHL is working on a number of things, a letter to the FDA. I'm encouraging all of our members to share whatever they're sending as part of the public comments to the FDA, and more to come on this.

DR. CALONGE: Thanks, Jelili. Sue?

DR. BERRY: I want to second or third the motion of what has been brought up. The SIMD, speaking on behalf of the SIMD, the SIMD is extremely concerned about the impact this will have, not only on newborn screening, but on almost all aspects of metabolic diagnostic testing.

And much of the ability that we have to care for children, and to provide adequate care may be in jeopardy. I don't think people realize the extent of even when a lab is using a kit that has FDA approval, almost always they modify its use to make it work in their lab.

And so, I think depending on how strict the enforcement gets, this could be an absolutely heart stopper for newborn screening, and for diagnostic testing. Almost all of the things that many of us do as geneticists and well as metabolic specialists.

DR. CALONGE: Thanks, Sue. Okay. So I just wanted to make a couple points as we close.

The Committee will be, just to remind you. Our discussion will be pausing on new nominations for at least six months while we continue to have additional opportunities to listen to stakeholders on the nomination process, and decision matrix and make decisions about those two areas.

In the meantime, nominators for potential conditions can contact HRSA staff about the timing, format and criteria for new nominations, so that we allow that middle ground that we talked about. I would also like to remind you that the meeting that is scheduled for February 2024, will most likely be scheduled at a different date, as we don't have a room, and it's an in person meeting.

And so, we think having the room could be important for that. So please before you make any arrangements for travel, and as you think about scheduling, keep a lookout for information regarding the next meeting on the ACHDNC website. I can guarantee you that it won't be sooner than the original February date. It will be sometime later.

Again, I want to thank everyone for your time, your invaluable contributions to the Advisory Committee, for your unwavering commitment to newborn screening, the mission and outcomes that we

are all invested in. And with that, the November meeting of the Advisory Committee is now adjourned. Thank you.

(Whereupon at 12:41 p.m. the Advisory Committee of the ACHDNC adjourned.)